DISSERTATION ON
"A STUDY ON RHINO-ORBITAL MUCORMYCOSIS-ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT"

Dissertation submitted in partial fulfillment of the regulations for the award of the degree of

M.S.DEGREE BRANCH – IV
OTORHINOLARYNGOLOGY

UPGRADED INSTITUTE OF OTORHINOLARYNGOLOGY
MADRAS MEDICAL COLLEGE
CHENNAI – 600003

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

MAY 2019

BONAFIDE CERTIFICATE

This is to certify that, Dr.Raghavi, postgraduate student (2016 - 2019) in the Upgraded Institute of Otorhinolaryngology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, has done this dissertation titled **"A STUDY ON RHINO-ORBITAL MUCORMYCOSIS- ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT**" under direct guidance and supervision in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. MGR Medical University, Chennai for M.S. Branch–IV Otorhinolaryngology Degree Examination.

Prof. Dr.R.Muthukumar, MS., DLO., DNB
Director
Upgraded Institute of Otorhinolaryngology,
Madras Medical College,
Rajiv Gandhi Govt. General Hospital,
Chennai-600003.

Dr.R.Jayanthi, MD., FRCP.,
Dean,
Madras Medical College,
Rajiv Gandhi Govt. General Hospital,
Chennai-600003.

CERTIFICATE

This is to certify that, Dr.Raghavi, postgraduate student (2016 - 2019) in the Upgraded Institute of Otorhinolaryngology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, has done this dissertation titled **"A STUDY ON RHINO-ORBITAL MUCORMYCOSIS- ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT**" under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. MGR Medical University, Chennai for M.S. Branch – IV Otorhinolaryngology Degree Examination.

Prof.Dr.F.Anthony Irudhayarajan, MS, DLO
Upgraded Institute of Otorhinolaryngology,
Madras Medical College,
Rajiv Gandhi Govt. General Hospital,
Chennai – 600003.

DECLARATION

I, Dr.Raghavi, solemnly declare that the dissertation titled "**A STUDY ON RHINO-ORBITAL MUCORMYCOSIS-ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT"** is a bonafide work done by me at, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof.Dr.F.Anthony Irudhayarajan, MS, DLO** Professor of Department of Otorhinolaryngology, Madras Medical College. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University towards the partial fulfilment of the requirements for the M.S. Branch – IV, Otorhinolaryngology degree examination.

Dr.Raghavi

Place: Chennai.
Date:

CERTIFICATE – II

This is to certify that this dissertation work titled "**A STUDY ON RHINO-ORBITAL MUCORMYCOSIS- ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT**" of the candidate Dr.Raghavi with registration number 221614005 for the award of M.S. Degree in the branch of Otorhinolaryngology. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from the introduction to conclusion pages and result shows 1% percentage of plagiarism in the dissertation.

Prof. Dr.N.F.Anthony Irudhayaraj MS, DLO
Upgraded Institute of Otorhinolaryngology,
Madras Medical College,
Rajiv Gandhi Govt. General Hospital,
Chennai – 600003

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to **Prof.Dr.R.JAYANTHI, MD, FRCP (Gasg),** The Dean, Madras medical college, for having permitted me to undertake this study.

First and foremost I like to express my immense gratitude to my guide **Prof.Dr.F.ANTHONY IRUDHAYARAJAN M.S., D.L.O.,** Professor, Upgraded Institute of Otorhinolaryngology, for his valuable guidance, suggestions, encouragement, motivation, constant supervision and help in conducting and fulfilment of this study.

I am immensely grateful to **Prof.Dr.R.MUTHUKUMAR M.S, D.L.O, DNB**, the Director and Head of Department, Upgraded Institute of Otorhinolaryngology, for his valuable support in conducting the study.

I express my sincere gratitude to **Prof.Dr.G.SANKARANARYANAN, MS., DLO., MNAMS.,** Dean, Govt. Villupuram Medical College and Hospital, Villupuram for his encouragement, motivation to conduct this study.

I am greatly indebted to **Prof.Dr.N.SURESH KUMAR M.S, D.L.O,** Professor, Upgraded Institute of otorhinolaryngology, who helped me in conducting the study.

I express my sincere thanks to **Prof.Dr.M.N.SHANKAR M.S., D.L.O.,** Professor, Upgraded Institute of Otorhinolaryngology, for his valuable support.

I express my sincere thanks to **THE SECRETARY AND CHAIRMAN, INSTITUTIONAL ETHICAL COMMITTEE,** Rajiv Gandhi Government General hospital, Madras Medical College.

I express my sincere thanks to all the assistant professors, for their thoughtful guidance throughout the work.

I thank all my colleagues and friends for their constant encouragement and valuable criticism.

Last but not the least, I express my gratitude for the generosity shown by all the patients who participated in the study.

I am extremely thankful to my parents for their continuous support.

Above all I thank the god almighty for his immense blessings.

LIST OF ABBREVIATIONS

RM	-	Rhino-maxillary mucormycosis
ROM	-	Rhino-orbital mucormycosis
ROCM	-	Rhino-orbito-cerebral mucormycosis
CT	-	Computerized Tomography
MRI	-	Magnetic Resonance Imaging
DM	-	Diabetes Mellitus
DKA	-	Diabetic Ketoacidosis
HPE	-	Histopathological Examination
KOH	-	Potassium Hydroxide

TABLE OF CONTENTS

S.NO	TITLE	PAGE NO.
1.	INTRODUCTION	
2.	REVIEW OF LITERATURE	
3.	AIMS OF STUDY	
4.	MATERIALS AND METHODS	
5.	RESULTS	
6.	DISCUSSION	
7.	CONCLUSION	
8.	ANNEXURES Bibliography Proforma Master chart Consent form Ethics committee certificate Plagiarism certificate	

INTRODUCTION

Fungi are a major part of the ecosystem. With over 50,000 fungal species identified in the world, they are integrated critically into the lifecycle from birth to death[1]. Only about 0.1% (over 250 fungal species) are recognized as human pathogens.[2] Their incidence and diversity has increased dramatically in recent years.[3]

Mucormycosis, a rare, potentially deadly infection , is caused by the fungus of the order Mucorales. But when it does occur, it is well remembered by those who have cared for the afflicted patient because of the speed with which it can progress. It has certainly earned the designation of the most acutely fatal fungal infection known to man.

Mucormycosis is best known for its rhino-cerebral presentation even though it can infect the lungs, central nervous system, gastrointestinal tract, skin etc. Progressing through the stages of rhino-maxillary, rhino-orbital and rhino-orbito-cerebral mucormycosis[4], it is rapidly fatal in 50 to 80%. It primarily affects immunocompromised patients, more commonly diabetics but seldom infects a healthy host..[5]

The clinical hallmark of invasive mucormycosis is tissue necrosis resulting from angioinvasion and subsequent thrombosis. In most cases, the infection is rapidly progressive and results in death unless underlying risk factors (i.e., metabolic acidosis) are corrected and

aggressive treatment with antifungal agents and surgical excision is instituted.[2]

This study is undertaken to assess the risk factors, clinical features, investigations, management, and outcome of rhino-orbital mucormycosis.

AIM AND OBJECTIVES

PRIMARY AIM

1) To study the association of diabetes mellitus with mucormycosis

2) To study the treatment strategies and their outcomes

SECONDARY AIMS

1) To study the Demographic data of rhino-orbital mucormycosis

2) To study the other risk factors associated with the outcome of mucormycosis

3) To study the best modality of investigation

REVIEW OF LITERATURE

Maureen M. Roden et al in their study on **Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases**[6] in 2005, analysed 929 mucormycosis patients reported in literature since 1885. A drastic increase in the number of patients especially in the last 2 decades was present with DM, the most common condition in each decade. Mean age was 38.8, with 65% male. Sino-nasal mucormycosis was the most common variant (39%). Diabetes mellitus was the most common underlying factor (36%) of which 48% had diabetic ketoacidosis. Other factors were malignancy (17%), solid organ transplantation (7%), and no underlying condition in 19%. Rhizopus was the most common species (47%) with mucor species (18%) Overall mortality was 54.5%. 64% were treated with some antifungal agent. Of this 62 % survived. 57% of those treated with surgery alone survived. But with combined surgical and medical therapy 70% survived. 26% received no treatment and only 3% survived.

W. Jeong et al in their study on **The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports**[7], in 2018 analysed 851 patients from 2000 to 2017. 34% were from Europe, 31% from Asia and 28% from North/South America. Median age was 51 years. 63% were men. Median time to diagnosis was 10 days. Diabetes was the most common

underlying condition (40%) of which 20% had diabetic ketoacidosis. 42% had hematological malignancies and 14% received solid organ transplant. Corticosteroid use was present in 33%. 34% had rhino-orbital-cerebral mucormycosis, 22% cutaneous and 20% pulmonary mucormycosis. ROCM was more commonly identified in diabetics (51%) than non-diabetics (23%). 88% had proven mucormycosis and 12% probably. Histopathology was done in 83% and culture in 69 %(of which 79% grew). Rhizopus species was the most common (48%). Overall mortality was 46%, highest in disseminated (68%) and lowest with cutaneous (31%)

Dora E. Corzo-Leo´n et al in their study **Diabetes mellitus as the major risk factor for mucormycosis in Mexico: Epidemiology, diagnosis, and outcomes of reported cases**[8] analysed the literature of 418 cases that occurred in Mexico between 1982 and 2016. A clinical algorithm for early diagnosis was devised in this study. Median age was 42 years with 54% males. 72% were diabetics, of which 42% had ketoacidosis. 18% had an underlying malignancy. 75% were sino-nasal mucormycosis. Histopathology was positive in 88%, cytology in 98% and culture in 71%. Rhizopus species were the most frequent isolates (59%) followed by Mucor spp (28%). Mortality rate was 51% (125/244). Combined treatment with surgery and antifungal agents was used in 77 % (162/209) of which 47% died. This strategy significantly improved mortality in ROCM. Antifungal therapy alone was used in 14% (29/209)

of which 76% died. 15 patients did not receive any treatment and there was 100% mortality.

A Chakrabarti et al **Invasive zygomycosis in India: experience in a tertiary care hospital**[9], 75 cases were reported from July 2006 to December 2007 with antemortem diagnosis in 81%. Rhino-orbito-cerebral mucormycosis was 48% - the most common variant. Uncontrolled diabetes mellitus (58%) with 38% having diabetic ketoacidosis were significant underlying condition in ROCM. Mean age was 33 years, male to female ratio 2.6:1. Orbital presentations were most common - ophthalmoplegia (75%), proptosis (72%), and loss of vision (61%). Fever was uncommon 44%. ROCM divided into three clinical stages based on the extent of involvement: stage I had signs and symptoms limited to the sino-nasal area, stage II had sino-orbital disease, and stage III had intracranial extension from sino-nasal disease. The overall mortality was 45%. The mortality rate was significantly high (85%), 11/13 in patients who were managed without surgical debridement. Patients in stage III had significantly higher (89%, p=0.018) mortality compared to stages I or II.

Jyoti Shailesh Kolekar published a study, **Rhino-cerebral Mucormycosis: A Retrospective Study**[10] in 2014. 20 diagnosed cases of rhino-cerebral mucormycosis, between February 2003 to January 2006, at two institutions, were included in the study. The study

evaluated the etiology, pathology, clinical features, diagnosis, the management, and complications. (10 men and 10 women). The median age was 60 years (range 24–80 years). 80 % had uncontrolled diabetes mellitus. Symptoms were fever (50 %), nasal discharge (60 %), black necrotic turbinates (50 %), palatal ulceration or perforation (10 %), septal perforation (10 %) ,periorbital or facial swelling (40 %), oedema of lids (40 %), chemosis (40 %),decreased vision (40 %), restricted movements of eyeball (40 %) ophthalmoplegia (30 %), headache (30 %), sinusitis (30 %), facial paralysis (10 %), and confusion (20 %). Systemic Antifungal Therapy- Amphotericin B was given depending upon extent and aggressiveness of disease in the dose of 5 mg/kg for a period of 6–12 weeks. Repeated surgical debridement of paranasal sinuses and orbital exenteration were done. Approaches used for debridement of paranasal sinuses were endoscopy (75 %), Caldwell Luc (20 %), lateral rhinotomy (10 %), and combined approach (20 %). Diagnostic nasal endoscopy was done twice a week to rule out recurrence. The overall survival rates were 55 %. Diagnostic nasal endoscopy was done during follow up. Recurrence rate was 20 %

A Bhansali et al published a paper, **Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes**[11] in 2003. A retrospective, non-comparative, interventional analysis of 35 patients with 23 men and 12 women. Mean age 47.3 years. 31 patients had diabetes mellitus. Ethmoidal (86%) and Maxillary (80%) sinuses

were most commonly involved. Sinusitis was present in 100%. Other symptoms were nasal discharge/ulceration 74%, facial swelling 46% facial nerve palsy 46%, facial anaesthesia (34%), palatal necrosis and altered sensorium 29%, fever 26%, ophthalmoplegia 89%, proptosis83% loss of vision 80%. Predictors for survival were the lag time between first symptom and treatment with Amphotericin B, facial and lid gangrene, hemiplegia and cerebral invasion. Poor prognosis was also present in patients with loss of vision, ophthalmoplegia, palatal necrosis, and altered sensorium at presentation.

Yoav P. Talmi et al in their study **Rhino-orbital and rhino-orbito-cerebral mucormycosis**[12] in 2002 analyzed 19 ROCM patients. Mean age 60 years, 10 men and 9 women. Mean Time from symptom onset to initiation of treatment ranged was 72 hours (12 hours to 1 week). The mean time from diagnosis to death was 4 days. All except 2 patients presented from August to December. 6 patients had mixed fungal infection. Overall survival was 47%. They concluded that in mixed fungal infection, the therapeutic approach does not change.

Abdollahi A et al Published an article on **Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis- A retrospective analysis**[13] in 2016. Retrospective analysis of 15 cases of ROCM from 2007 to 2013 was done. The mean age of the patients was 54±11 years; Male: female ratio of 1: 2.7. Uncontrolled diabetes was

present in 13/15(86.7%). The maxillary sinus was most frequently involved (66.7%) followed by ethmoid sinus. Orbital involvement was present in 40% of the patients. Amphotericin B in combination with surgical debridement was used in the treatment of 80% of the cases. 73.3% of the patients who were diagnosed early and underwent medical and extensive surgical debridement of the infected tissues survived.

Michele D. Mignogna et al in their study **Mucormycosis in immunocompetent patients: a case series of patients with maxillary sinus involvement and a critical review of the literature**[14] analysed 212 immunocompetent cases of mucormycosis from January 1978 to June 2009. India had 44.3% of the cases followed by USA and Australia (19% each). Cutaneous mucormycosis (42.5%) was the most common followed by ROCM (38.2%). Mean age was 54.5 years. 4 female and 1 male. All were localised to maxillary sinus and completely treated.

Tumuluri Sravani et al **Rhino-cerebral mucormycosis: Pathology revisited with emphasis on the perineural spread**[16] **– 2017 –** 30 patients (20 males and 10 females) with 50 years median age. On histopathological examination, suppurative inflammation with a predominance of neutrophils was seen in 25 biopsies and Suppurating granuloma with neutrophils, lymphocytes, and foreign body giant cells in 3 biopsies. Angioinvasion was noted in 25 and soft tissue invasion in

20 biopsies. Peripheral nerves were identified in 19 biopsies and in which perineural spread was identified in 15.

Seid Mousa Sadr Hosseini et al **Rhino-cerebral mucormycosis: pathways of spread**[17] – 2004 Prospective study of 10 patients of RCM. The median age of 45.6 years. The average time interval between symptoms and surgery was 6 days. Predisposing factors were diabetes in nine patients and drug-induced immunodeficiency in one patient. DKA was present in 4/9 and renal failure in 2/9. They proposed that pterygopalatine fossa as the main reservoir for RCM, and extension into the orbit and facial soft tissues followed this route via pterygopalatine fossa, inferior orbital fissure and then the retro-global space of the orbit. Thus debridement of the pterygopalatine fossa was proposed as the definitive method of managing this infection. Behind the intact posterior wall of the maxilla, they found avascular greyish fungi replacing the fat and thrombosis of the internal maxillary artery.

Héctor Manuel Prado-Calleros et al - **Rhino-Orbital Mucormycosis. A cohort study of its treatment according to disease extent and reversion of its pathophysiology**[18] – 2016 - A comparative cohort study between debridement of the pterygomaxillary fissure and orbital exenteration if needed with a historical group where these criteria were not applied. 15 cases with 8 in historic group A and 7 in study group B. In both groups, Amphotericin B was given. In group

B, surgical treatment with extensive debridement including exploration of the pterygomaxillary fossa with orbital exenteration in patients who presented orbital apex syndrome was included. In group A, the mortality rate was 50%, in group B all patients were clinically cured.

Peter Raab et al **Imaging Patterns of Rhino-Orbital-Cerebral Mucormycosis in Immunocompromised Patients - When to Suspect Complicated Mucormycosis**[19] 2017 - Retrospective analysis of imaging findings of 8 patients with proven mucormycosis was studied. MRI and CT images were classified as abnormal or normal with respect to paranasal, orbital and cerebral signal results. Unexpectedly 7/8 with abnormal findings of paranasal sinuses and adjacent tissues showed no bony sinus wall destruction. 7/8 showed inflammatory changes in the infratemporal fossa and facial/periorbital tissues. 3/8 had an invasion of the cavernous sinus and carotid artery. Only one patient had a local infection of the hard palate.

Jorge L. Gamba et al **Craniofacial Mucormycosis: Assessment with CT**[20] **-** CT scans of 10 patients with RCM were reviewed. Early features present as mucosal thickening on CT, usually without air/fluid levels. Evidence of bone destruction, seen in only two patients, was a late finding. Usually, it was absent despite deep extension of disease beyond the bony confines. Intracranial mucormycosis usually involves the base of the brain and cerebellum through the infratemporal fossa or

orbit. Intracerebral fungal abscess appeared as low-density masses with variable peripheral enhancement on CT scans. Obliteration of normal fat density within pterygopalatine fossa, pterygomaxillary fissure or infratemporal fossa suggests a deep extension of infection. 5 had infratemporal fossa involvement and 4 had pterygopalatine fossa involvement.

Kshitij Shah et al - **Orbital Exenteration in Rhino-Orbito-Cerebral Mucormycosis: A Prospective Analytical Study with Scoring System**[22] – 2018 15 patients were included. Sion Hospital Scoring System was devised based on 3 main criteria, namely: (1) clinical signs and symptoms. (2) Direct and Indirect Ophthalmoscopy. (3) Imaging 1 point = Mild symptoms/signs; 2 points = Moderate symptoms/signs; 3 points = Severe symptoms/signs for each category. Depending on the score, surgical debridement ± orbital exenteration was done within a period of 24–36 h of admission. Inj Amphotericin-B intravenously was given at strength of 1 mg/ kg/day till a total dose of 2–3 g was completed. Above the score of 23 patients were taken up for orbital exenteration.

Andrew Blitzer et al – **Patient Survival Factors in Paranasal Sinus Mucormycosis**[23] - 1980 – 179 cases were analysed – 170 from literature and 9 cases of their own. Mean age 39 years. Clinical features like hemiplegia, facial necrosis, palatal necrosis, ophthalmoplegia,

decreased vision, and nasal deformities showed markedly poorer prognosis. The most important determinant was the underlying disease and the rapidity with which they can be reversed. Extremely poor prognosis of patients with leukemia, infant diarrhoea, renal disease. The use of Amphotericin B and surgical debridement was considered as an important determinant for survival. 50% overall mortality. Diabetics among the survivors were 75/90(83%), among the fatalities were 51/89(56%). Age, sex, laterality, radiographic findings were not related to outcome.

Olga Plowes Hernández et al **- Rhino-Orbito-Cerebral Mucormycosis. Management Strategies to Avoid or Limit Intracraneal Affection and Improve Survival**[24] – 2015 – A retrospective, longitudinal, descriptive study, January to October 2013 of 5 cases. Mean age was 57 years. 1.5:1 male: female ratio. All patients had uncontrolled diabetes mellitus. 60% had orbital apex syndrome Disease in the Pterygomaxillary fossa was found in 100% of the patients and in the infratemporal fossa in 60%. Early extensive endoscopic debridement (including pterygomaxillary fossa) and orbital exenteration in patients presenting with orbital apex syndrome was doneand all those patients survived.

ANATOMY

MAXILLA

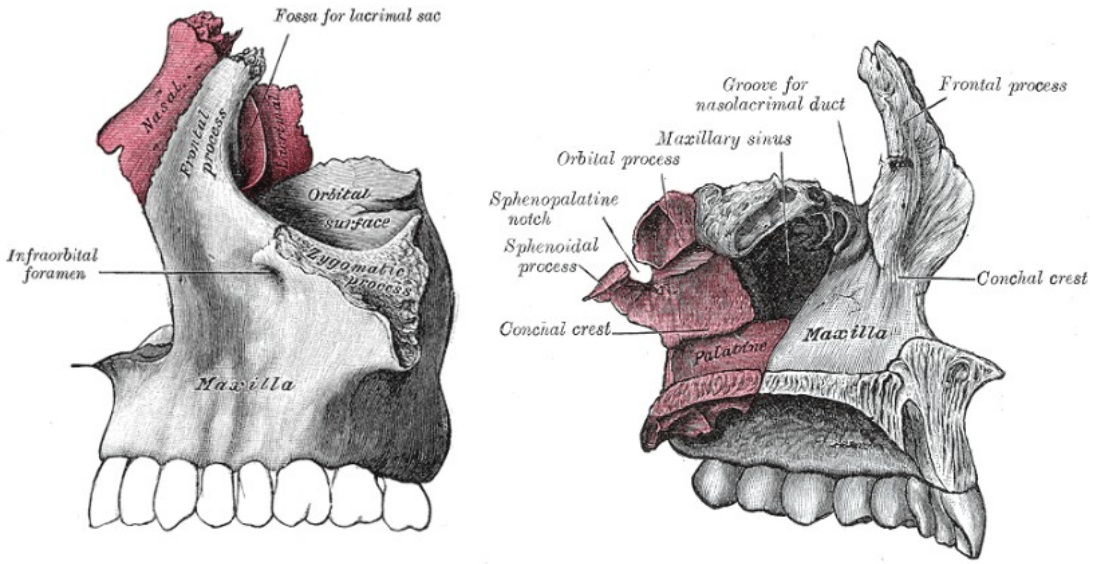


Fig 1: Maxilla Osteology – Lateral and Medial views

SURFACES AND RELATIONS

- ❖ Anterolateral surface – cheek
- ❖ Posterior surface – Infratemporal fossa and Pterygopalatine fossa
- ❖ Medial surface – Lateral wall of the nasal cavity
- ❖ Superior surface – Floor of orbit

PROCESSES

- ❖ Frontal process
- ❖ Zygomatic process
- ❖ Alveolar process
- ❖ Palatine process

PTERYGOPALATINE FOSSA

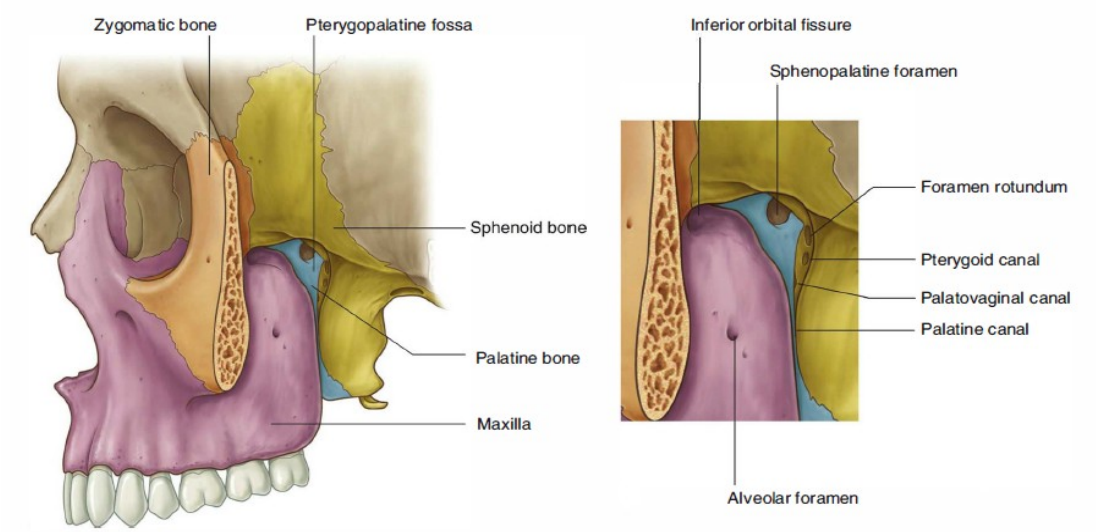


Fig 2: Pterygopalatine fossa – Boundaries and Foramina

BOUNDARIES

- ***Anteriorly:*** Posterior wall of maxilla
- ***Posteriorly and Superiorly:*** Sphenoid bone
- ***Medially:*** Lateral surface of the palatine bone with its orbital and sphenoidal process

Table-1: Communications

Foramen	Structure passing	Communication to
Foramen Rotundum	Maxillary nerve	Middle cranial fossa
Pterygoid canal	Vidian Nerve and artery	Middle cranial fossa
Inferior Orbital fissure	Inferior orbital nerve	Orbit

Foramen	Structure passing	Communication to
Palatovaginal canal	Pharyngeal artery and nerve	Nasopharynx
Sphenopalatine foramen	Sphenopalatine artery	Nasal Cavity
Pterygomaxillary fissure	Internal maxillary artery	Infratemporal fossa
Palatine Canal	Descending palatine artery	Palate

Contents - Maxillary artery and its branches; Pterygopalatine ganglion; Maxillary nerve; Pterygoid plexus of veins; Fat; Lymphatics.

ORBIT

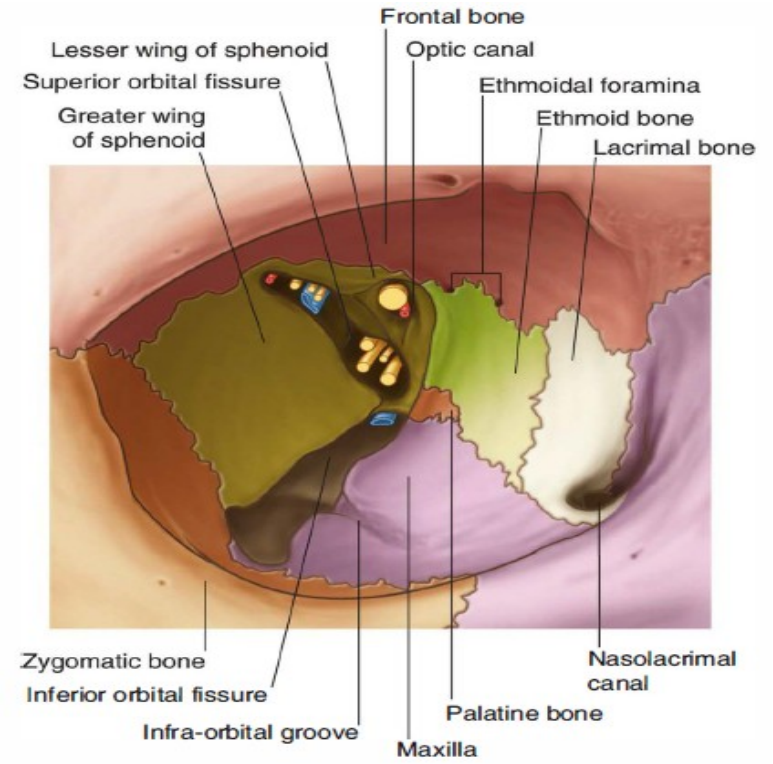


Fig 3: Orbit Osteology

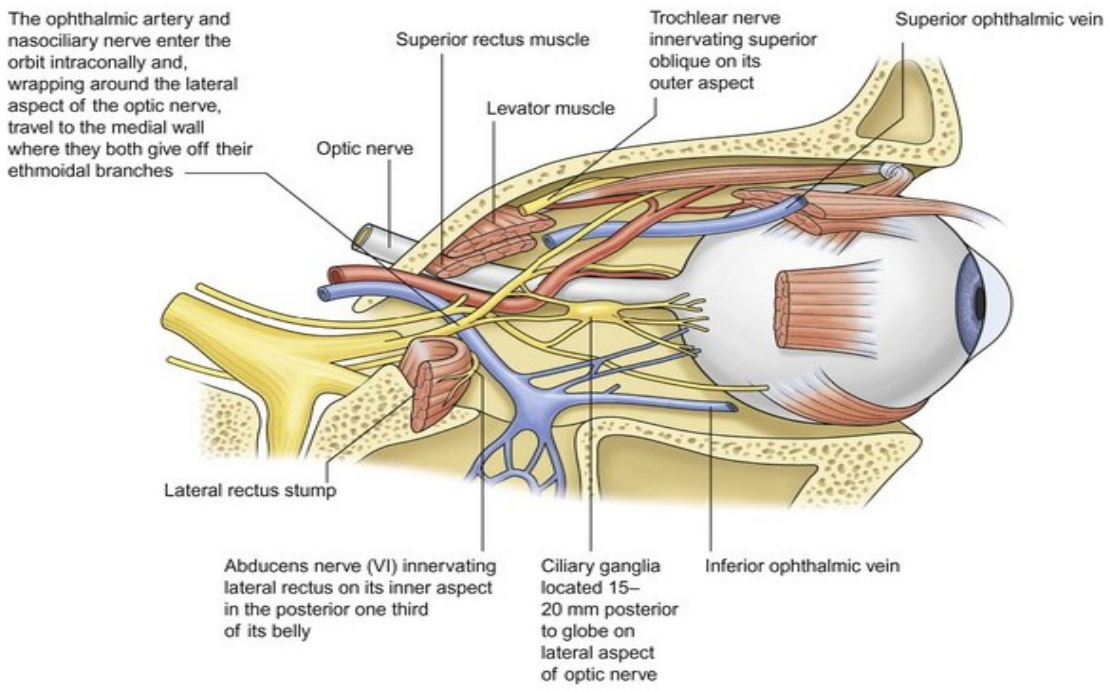


Fig 4: Orbital Contents

MICROBIOLOGY

Fungi are eukaryotic organisms that evolved shortly before plants and animals. Fortunately, only a few hundred species are implicated in human disease, of which only a few dozen fungi cause 90% of human infections. Most pathogenic fungi are exogenous, residing in water, soil, and organic debris. They can cause disease by inducing an allergic response, elaborating toxin, establishing an infection or invading tissues. Most of the fungal rhinosinusitis is caused by species of Aspergillus, dematiaceous (i.e., melanized) moulds, or Zygomycetes which are part of the normal microbial flora.[3]

Most fungi are obligate or facultative aerobes. All fungi have an essential, rigid cell wall that determines the shape of the fungus. Cell walls are composed largely of carbohydrate layers and long chains of polysaccharides, as well as glycoprotein and lipid. Cell wall polysaccharides may activate the alternative pathway of the complement cascade to stimulate an inflammatory reaction, release immunodominant antigens that may elicit cellular immune responses and diagnostic antibodies.[3]

In addition to their vegetative growth as yeasts or moulds, fungi can produce spores to enhance their survival. Spores can be readily airborne and dispersed. They are more resistant to adverse conditions and can germinate when conditions for growth are favourable. Spores can derive from asexual or sexual reproduction. The medical fungi produce two major types of asexual spores, conidia, and in the Zygomycetes, sporangiospores. [3]

The outcome of inhaling an inoculum of spores depends upon several factors: (1) the number of spores inhaled; (2) the size of the fungal particles, which influences the depth to which they penetrate the nasal or respiratory passages; (3) the integrity of the nonspecific and specific host defences; and (4) the pathobiologic potential or virulence of the particular fungus.

During infection, most patients develop cellular and humoral immune responses to the fungal antigens. Pathogenic fungi do not produce potent toxins, and the basis of fungal pathogenicity is poorly understood.[3]

Many cases of fungal rhinosinusitis are characterized by colonization rather than invasion (i.e., non-invasive disease). Tissue invasion by fungi also stimulates the host defences, which may ultimately kill or contain the fungal cells.[3]

Certain risk factors are well associated with specific mycotic infections, such as atopy with allergic fungal sinusitis, or diabetic ketoacidosis with rhino-cerebral mucormycosis. Most mycoses are difficult to treat.[3]

MUCORMYCOTINA

A comprehensive phylogenetic re-analysis of the Fungi kingdom, based on molecular methods, resulted in the reclassification of the polyphyletic phylum Zygomycota into the phylum Glomeromycota, which inturn was divided into four subphyla: Entomophthoromycotina, Mucoromycotina, Kickxellales, and Zoopagomycotina. The mucormycetes belong to the order Mucorales and involve 6 main families Syncephalastraceae (Genus Syncephalastrum), Saksenaeaceae (genera Saksenaea and Apophysomyces) Cunninghamellaceae (genus Cunninghamella), Mucoraceae (genera Mucor, Rhizopus, Rhizomucor

and Actinomucor), Thamnidiaceae (Cokeromyces) and Lichtheimiaceae (genus Lichtheimia). About 70% to 80% of mucormycosis are caused by fungi belonging to genera Rhizopus, Mucor and Lichtheimia.[25]

PATHOGENESIS

Medically important members of the order Mucorales share many features with other filamentous fungi such as portals of the host for infection (airways and disrupted mucocutaneous barriers), the main lines of innate host defences (phagocytes, specific ligands in fungal spores such as pathogen-associated molecular patterns (PAMPs) and immune cells such as Toll-like receptors (TLRs)), as well as histopathological and clinical features. However, some Mucorales also possess unique virulence characteristics and exert distinctive host-pathogen interactions, thus, causing host evasion and disease progression.

Mucoromycotina have a lot more genes encoding for lytic enzymes than other fungal pathogens. Hyperglycaemia common feature in mucormycosis patients can cause excessive glycosylation of proteins such as ferritin and transferrin. This in addition to low pH strongly impairs their ability to chelate iron. Low serum pH affects both the phagocytic effect of macrophages and the chemotactix and oxidative burst of neutrophils. Thus it diminishes the main host defenses against the invasion of mucormycetes.[26] Other reasons may be poor

recognition, reduced uptake and a low cytokine response to fungi in diabetic patients.[48]

One hallmark of mucormycosis is angioinvasion, and the ability of a fungal pathogen to invade host cells is a putative virulence factor. Recently, the glucose-regulated protein 78 (GRP78) has been identified to enable adherence and invasion of the pathogen into the endothelial cell via an endocytotic mechanism.[27]

Another virulence factor is the iron acquisition. R. oryzae lacks genes for non-ribosomal peptides, the enzymes that produce hydroxamate siderophores. It therefore fully depends on rhizoferrin, which is less efficient, reductive iron assimilation by rFTR1 (iron permease, a cell membrane protein) and possibly iron acquisition through degradation of heme by heme oxygenase. Mutation of rFTR1 thus results in decreased virulence.[27]

In the most commonly encountered clinical setting, spread occurs by invasion of local vessels and via direct extension through the cribriform plate into the central nervous system. Retrograde extension of the fungi into the brain by means of the nerves is another plausible mechanism.[29] Perhaps the perineural sheath of loose connective tissue merely represents a ‘‘path of least resistance’’ compared to the surrounding tissues. However, different mechanisms must exist for vascular invasion, as blood vessel walls are denser than fascia.[29]

MANIFESTATION OF THE DISEASE

There are five recognized forms of fungal sinusitis, each with its own pathophysiology and clinical presentation. They include acute fulminant invasive fungal sinusitis, chronic invasive fungal sinusitis, granulomatous invasive fungal sinusitis, fungus ball, and allergic fungal rhinosinusitis (AFS).

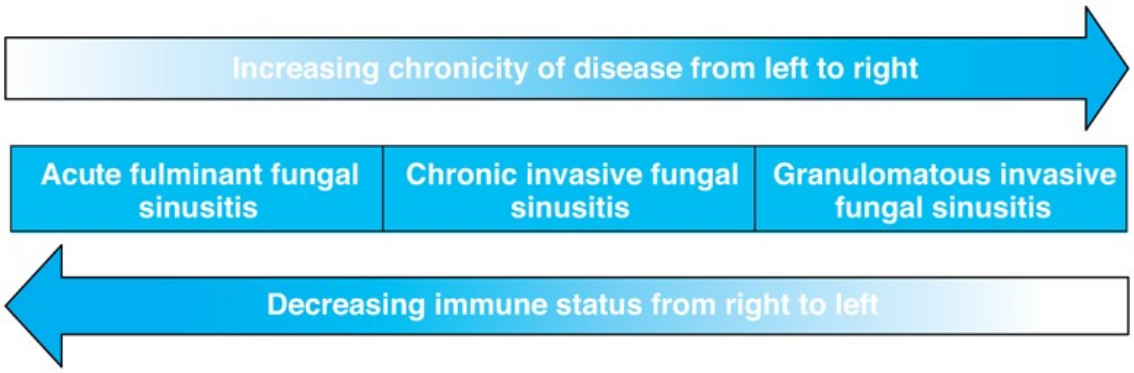


Fig 5: Types of Invasive fungal sinusitis

Fungus balls caused by mucormycosis are quite rare. In a diabetic patient, it warrants surgical removal. The patient probably should be covered perioperatively with Amphotericin B to prevent the development of invasion with the trauma and mucosal breaks that occur with surgery.[4] Likewise, saprophytic cases may occur. If a patient has an asymptomatic sporulating mass on a crust within the Sinonasal cavity and has no symptoms of an invasive disease, particularly no anaesthesia, and there is no source of immunocompromise, then no further therapy is required beyond cleaning of the sporulating crust. Rare cases of allergic fungal sinusitis associated with Mucor species have been reported.[4]

Type	Course	Immune status	Fungus	Pathology	Characteristic clinical features	Prognosis	Treatment
Acute fulminant	Short <4 weeks	Immunocompromised with debilitating medical illness	Mostly Mucor Occasionally Aspergillus	Necrosis, vascular invasion	Black eschar	Poor	Radical debridement & antifungal
Chronic invasive	Slow >3 months	May be immunocompromised Common in patients with uncontrolled diabetes	Commonly Aspergillus	Necrosis, inflammatory exudate, vascular invasion	Early eye symptoms in a clinical setting of acute sinusitis	Good with aggressive surgical and medical therapy	Radical surgery & antifungal
Granulomatous	Chronic indolent	Immunocompetent/ healthy	Aspergillus	Giant cell reaction to fungus	Firm swelling causing proptosis	Good but strict follow-up required	Surgery & antifungal

Fig 6: Types of invasive fungal rhinosinusitis and their salient features

Mucormycosis may have an acutely fulminant course or a slower indolent invasive course. When the source of immunocompromise is great, the rapidity of progression is great, whereas in cases of no or mild immunocompromise, indolent invasive clinical pictures emerge.

DIAGNOSIS OF MYCOTIC INFECTIONS

In the diagnosis of fungal infections, the following laboratory strategies may be employed: (1) microscopic examination of fresh clinical specimens or histopathological preparations; (2) culture of the etiologic agent from clinical material; (3) serology and skin testing; (4) radiographic techniques; (5) polymerase chain reaction (PCR) methods to detect specific fungal DNA in clinical specimens.[3]

Fungal disease is determined to be invasive if it meets the following criteria on histopathological examination: (1) hyphal forms

within the submucosa with or without angiocentric invasion; and (2) tissue necrosis with minimal host inflammatory cell infiltration[5]

MICROSCOPIC EXAMINATION

Mycology laboratories traditionally use the potassium hydroxide (KOH) method, which gradually dissolves human material and makes fungal cells easier to see. Since the sensitivity of this method is relatively low, phase contrast microscopes can be used for the same.[31] But the ideal stain for the direct examination is a mixture of KOH and calcofluor white. This requires a microscope with ultraviolet illumination at the appropriate wavelength.[3] Calcofluor white stains fungal cell wall polysaccharides non-specifically and vastly increase the sensitivity. Other optical brighteners, such as Blankophor (AG Scientific, San Diego, CA), can also be used in the same way.[31]

Fungal cells also can be seen with a Gram stain.[3] Gram reagents may stain fungal cytoplasm, but they do not stain the fungal cell wall. Because there may be very little cytoplasmic content in many cells, and they are not seen.[31] Exudates, as well as tissue, can be stained with routine HPE preparations, such as haematoxylin and eosin (H&E), Gomori methenamine silver (GMS), or periodic acid-Schiff (PAS). The GMS and PAS stain the fungal cell walls black or red, respectively.[3] HPE techniques are more time-consuming. But they provide the only means of determining whether a fungus is invading into host tissue.

They have the advantages of producing permanent preparations that can be viewed at any time, studying human tissue reactions and of allowing differential staining methods. The H&E stain can be useful are for the hyphae of Rhizopus and Aspergillus species as they stain well in it.[31]

The majority of fungal agents of rhinosinusitis present as hyphae. Mucorales have been classically described as having broad (10–50 microns), ribbon-like aseptate hyphae with right-angled branching. But the hyphae are actually pauciseptate, and the angle of hyphal branching can vary from 45 to 90°. This paucity of septation causes an absence of internal support in the broad hyphae, and allows them to become collapsed, twisted, and folded in a characteristic ribbon-like fashion.[31] Inflammatory tissue reaction is variable and reflects the host's immunologic status. Usually edema and necrosis with accumulations of neutrophils, plasma cells, and sometimes giant cells are seen.[4] Angioinvasion with surrounding tissue infarction and occasionally perineural invasion are observed.[29,32]

On frozen section, Aspergillus hyphae may be mistaken for mucormycosis because of artefactual swelling. On permanent sections, the distinction between the two usually can be made, because Aspergillus hyphae are narrower, regular, frequently septated, and branch at 45°.[4]

Neither frozen section nor special stains will definitely distinguish among fungal species, but this distinction can generally be made on permanent histopathological sections.[33] If fungal spores are present, distinctive features, such as their size, shape, surface texture, and the number of cells may permit the identification of their genus.[3]

Immunofluorescence reagents for staining of fungi in tissue have been developed for agents of fungal sinusitis, including Rhizopus species but are not commercially available.[31]

Mucorales grow on most routine bacterial (i.e. sheep blood agar, chocolate agar) and fungal culture media (i.e. Sabouraud dextrose agar, inhibitory mould agar, potato dextrose agar) at a wide range of temperatures, 25–55°C. Antibacterial antibiotics (e.g., gentamicin, chloramphenicol) and cycloheximide can be to the media to inhibit bacteria and saprophytic moulds, respectively.[3] They form fluffy white, grey, or brownish colonies that rapidly fill the Petri dish within 1–7 days.

The fungal cultures may take days to weeks to grow or fail to grow if the patient is already on systemic antifungal agents (false-negative). False-positive growth can also be present. Fungal culture to optimize antifungal agent selection[30] and for epidemiological purposes.

The DNA-based molecular techniques include Conventional PCR, RFLP, DNA sequencing and Real-time PCR.[34] Species identification can also be done using this method. But they are not universally available.

IMMUNODEFICIENCY

Innate immunity is the first-line defense against all pathogens, but patients with defects of innate immunity tend to be particularly susceptible to recurrent bacterial abscesses and to local and disseminated fungal infection. Humoral immunity is predominantly involved in neutralization of soluble viral particles and the killing of extracellular bacteria. Cell-mediated immunity is important in the defense against protozoa, fungi, viruses, mycobacteria, and other intracellular bacteria.[35]

The risk factors include long-term antibiotic usage, indwelling catheters, nasal intubations, immunosuppressant drugs, steroids, metabolic abnormalities (e.g., diabetic ketoacidosis), prolonged hospitalization, diabetes mellitus, prolonged neutropenia, sinus disease etc.[36]

Patients with a hematologic disease are at highest risk during the neutropenic period. The duration of neutropenia and absolute neutrophil counts below 500 cells/ml strongly correlated with the development of

an invasive fungal disease. [5] Bone marrow transplant recipients are at greatest risk in the immediate post-transplant period before engraftment and in the setting of graft versus- host disease (GVHD). After solid organ transplantation the first 100 days constitute the critical period.[37]

Over-colonization of the sinuses by fungi and mucosal modification by microbia, allergic or virus can lead to opportunistic and lethal infections.[36]

Preventive measures include (1) decreasing exposure to pathogenic fungi and (2) the use of prophylactic antifungal agents (3) Surveillance.

TREATMENT

The principles of treatment for mucormycosis of the paranasal sinuses are the reversal of immunocompromise, systemic antifungal therapy, and radical surgical debridement. Time is a very important issue. But, if the source of immunocompromise cannot be reversed, then the other adjuncts are almost always ineffectual.[4]

Surgical debridement (1) it slows the progression of the disease; (2) it reduces fungal load; and (3) it provides a specimen for culture.

Surgical treatment of mucormycosis has evolved from external techniques, such as Caldwell-Luc procedures, and external

ethmoidectomy to endoscopic diagnosis and debridement. Radical resections (radical maxillectomy, craniofacial resection, and orbital exenteration) to remove disease outside the sinonasal cavity rarely achieve negative margins or improve long-term survival. Orbital exenteration was once advocated for ocular involvement especially if blindness had occurred. This is now controversial.[4]

Early aggressive debridement should be performed on all patients with a biopsy-proven disease or any patient suspected of having an invasive fungal disease[5] and extended until clear bleeding margins are exposed. A second-look procedure should be scheduled within 48 to 72 hours if residual disease in the Sinonasal cavity is suspected. Follow-up consists of weekly rigid nasal endoscopy until reversal of immunocompromise and should be once a month for 6 months thereafter. Ultimately a patient's infection can be considered resolved if there is no evidence of disease on nasal endoscopy or CT scan.[36]

Reversal of underlying immunocompromised state is one of the most important factors. Strict glycaemic control and stabilizing the metabolic state greatly improves the survival rates. Surgery does not prolong survival in neutropenic patients who do not recover their white blood cell count. Granulocyte colony-stimulating factor (GCSF) has been shown to be efficacious for promoting bone marrow recovery in neutropenic patients. [5] Since diabetes mellitus and acidotic states are

far more easily stabilized compared to hematological malignancies or neutropenic deficiencies, they have a better outcome comparatively.

ANTIFUNGAL AGENTS

Fungi, like their human hosts, are eukaryotic organisms with similar macromolecular processes. Hence unique targets for chemotherapy are challenging to find.

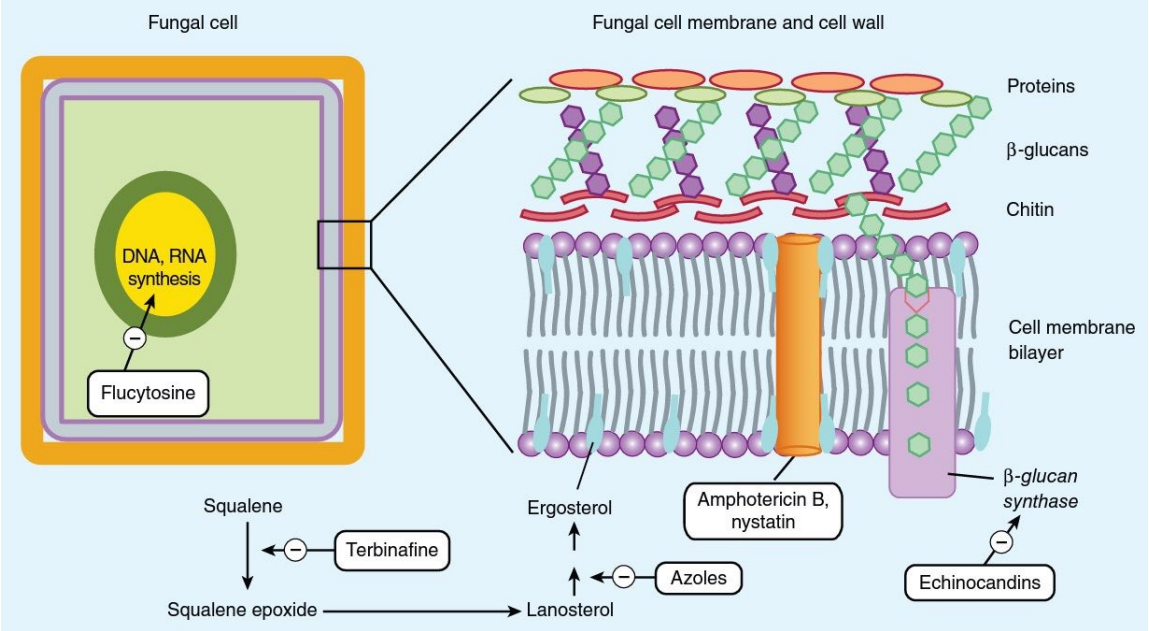


Fig 7: Site of action of various antifungal agents

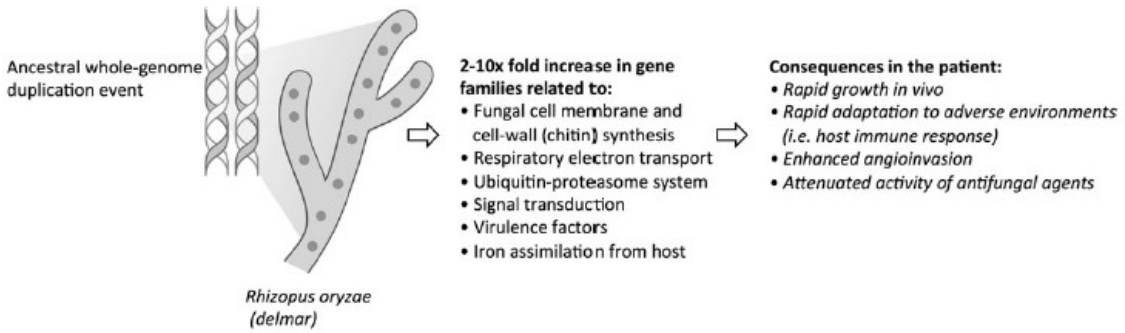


Fig 8: Genetic Differences between Mucormycosis and Aspergillus

AMPHOTERICIN B DEOXYCHOLATE

Introduced into clinical practice over 50 years ago, Amphotericin B (a polyene macrolide) remains the standard drug for most life-threatening systemic fungal infections.[1] It has a broad spectrum of coverage but also has significant toxicities that limit its use to the most difficult infections.[2]

The mechanism of action is to bind preferentially to ergosterol, a protein found in fungal cell membranes, increase its permeability causing leakage of intracellular components and ultimately cell death. Even though ergosterol is not present in bacterial or human membranes[2], Amphotericin B binds to a lesser degree to cholesterol in mammalian cell membranes, which probably accounts for its toxic effects on human cells.[1]

Administered orally, Amphotericin B exhibits minimal absorption (less than 5%) and can be used for bowel decontamination of fungi.[1] Intravenous doses in the range of 0.25 to 1.2 mg/ kg once daily (most commonly 0.4 to 0.7 mg/kg/d) in 5% dextrose solutions[1] over 2 to 4 hours (for systemic or invasive disease) or orally as a lozenge or in a 100-mg/mL solution taken four times per day (for topical infections).[2] A total dose of 2 to 4 g over six to eight weeks.[33]

It has a large volume of distribution of 4 L/kg which follows a three-compartment model with high concentrations reaching the liver,

spleen, lungs, kidneys, muscle, skin, and adrenal glands. The degree of protein binding is approximately 91% to 95%. Concentrations of Amphotericin B in the peritoneal, pleural, and synovial fluids to be approximately half the concentrations measured in serum or less. Cerebrospinal fluid values range from 2% to 4% of the serum concentrations.[1]

Metabolism is not clearly understood. Metabolites have not been identified. Blood levels are not affected by hepatic or renal failure. Following a biphasic elimination pattern, the initial half-life ranges from 24 to 48 hours, with a subsequent terminal half-life of up to 15 days.

Because of hypersensitivity reactions, a test dose (l mg in 50 mL of 5% dextrose over 20 minutes) is recommended. The dose of Amphotericin B is not modified for patients with renal insufficiency till creatinine rises above 3g/dl. Alternative regimens with alternate daily dosing can be used. Infusion-related reactions, characterized by rigors, chills, fever, headache, nausea, malaise, and generalized aches, are acute in onset and extremely common (>50%). Premedication with NSAIDs or hydrocortisone (25 mg added directly to the infusion) may help diminish this reaction. Thrombophlebitis, which is also common, can be minimized by decreasing the rate of infusion, adding small amounts of heparin to the infusion (1000 units /L), using a central line, rotating the

infusion site, and avoiding highly concentrated preparations of Amphotericin B.[1]

Nephrotoxicity may occur in up to 80% of the patients, manifested by azotemia, electrolyte wasting (K+ and Mg2+), and a decrease in urinary concentrating ability. Renal tubular acidosis may also be associated. These are usually reversible even following high cumulative doses, but rarely persistent. A total dose greater than 4 to 5 g may have a permanent renal impairment. Sodium supplementation to maintain intravascular volume and inhibit the tubuloglomerular feedback system is given before or after Amphotericin B infusion.[1]

Reversible Normochromic, normocytic anaemia with decreases in hemoglobin of up to 35% from baseline can occur following extended therapy due to direct suppression of erythropoietin production or deteriorating renal function.[1]

The proposed mechanism for resistance is an alteration in ergosterol synthesis or multiple drug resistance (MDR) pumps could be involved.[1]

Amphotericin B remains the treatment of choice for most progressive life-threatening fungal infections, including invasive aspergillosis, zygomycosis, and severe infections of blastomycosis, coccidioidomycosis, sporotrichosis, and histoplasmosis. Amphotericin B

plus flucytosine is the drug combination of choice for the treatment of cryptococcal meningitis. Intrathecal administration has been used in patients with severe or refractory coccidioidal or cryptococcal meningitis. Intraperitoneal administration and intravitreal Amphotericin B have also been used.[1]

Lipid-Based Formulations of Amphotericin B are differenent in their pharmacokinetics. These are preferentially delivered into reticuloendothelial tissues, such as the liver and spleen, and, to a lesser extent, the lungs. Doses for these preparations are 1 to 5 mg/kg (liposomal Amphotericin B), 5 mg/kg/d (ABLC) and 3 to 5 mg/kg (ABCD). More dosage of Amphotericin B can be given safely for individuals unable to tolerate the nephrotoxicity or other serious drug interactions. These preparations are probably the drugs of choice for rhino cerebral zygomycosis, which requires administration of high doses of polyenes after surgical debridement.[1]

The topical preparation attempts to limit side effects. Adverse drug effects include local irritation (nasal burning, dryness, bleeding, itching), muscle aches, facial pain, nasal congestion, rhinorrhoea, and respiratory symptoms (asthma attack, bronchitis, cough). Currently, topical antifungal therapy is primarily used adjunctively in invasive fungal sinusitis. Though it has not been studied systematically, due to the small risk associated with the administration it is often employed

adjuvantly. [38] The topical application of Amphotericin B is a 50 mg vial of intravenous Amphotericin B and 10 mL of sterile water (not saline or dextrose). This also can be nebulized into the nose with a Rhinoflow device in dosage is 4 mL in each nostril 2 to 6 times daily.[4]

AZOLES: IMIDAZOLES AND TRIAZOLES

Imidazoles (clotrimazole, ketoconazole, miconazole) and triazoles (fluconazole and itraconazole) are fungistatic agents without serious nephrotoxic effects. They act by inhibiting the cytochrome P-450 dependent enzyme lanosterol 14-a-demethylase, which is necessary for the conversion of lanosterol to ergosterol causing significant damage to the cell membrane by increasing its permeability and ultimately causing cell lysis and cell death.[1]

Itraconazole has the best activity against fungi such as Aspergillus and black moulds that typically cause fungal sinusitis. But it is an inappropriate agent for rhino-cerebral mucormycosis, which requires a-Amphotericin B or its lipid preparations. Dosages of itraconazole range from 100 to 400 mg per day. The most common side effect is gastrointestinal upset. Others are rash, headache, mild elevations in liver function tests.[1]

Isavuconazole (Cresemba) is a novel triazole antifungal agent that was approved for the treatment of mucormycosis in March 2015.[39]

Posaconazole, another triazole antifungal, is used for off-label salvage treatment of mucormycosis in patients intolerant to a-Amphotericin B. It has been shown to be superior to fluconazole or itraconazole as prophylaxis against invasive mould infection (both aspergillosis and mucormycosis).[39]

Voriconazole (a derivative of fluconazole) is more effective for invasive aspergillosis than for mucormycosis.[39]

OTHER ANTIFUNGAL AGENTS

The echinocandins are a new class of antifungal agents that possess a novel mechanism of action by inhibiting 1,3 B-glucan synthesis a critical component for maintenance of cell wall integrity.[1] They are used as combination therapy in mucormycosis.

Terbinafine, (inhibits production of ergosterol), Flucytosine, (interrupts DNA synthesis), nikkomycin, (inhibits protein synthesis) and dicationic aromatic compounds (a series of fungicidal peptides) have no action against mucormycosis.

Simultaneous targeting of the cell membrane, cell wall, and signal transduction pathways involved in fungal homeostatic responses (e.g., protein kinase C or the calcineurin pathway) may prove to be an important strategy for improving drug activity in this remarkably adaptive pathogen.[40]

MATERIALS AND METHODS

Study Period	**:**	June 2016 to September 2018
Study Design	**:**	Prospective Observational Study
Study Place	**:**	Rajiv Gandhi Government General Hospital, Chennai
Collaborating Department	**:**	Upgraded Institute of Otorhinolaryngology
Ethics Committee Clearance	**:**	Obtained
Sample Size	**:**	50
Data Collection	**:**	Clinical

BENEFIT TO THE COMMUNITY

- ❖ Awareness of risk factors of mucormycosis
- ❖ Awareness regarding early diagnosis and prompt treatment
- ❖ Reduction in mortality

Conflict of Interest	**:**	**Nil**
Financial Support	**:**	**Nil**

INCLUSION CRITERIA

- All patients presenting to the ENT Department with rhino-orbital mucormycosis.
- Histological / KOH smear positive for Mucormycosis
- Understands the protocol and is able to give informed consent.

EXCLUSION CRITERIA

- Patients not willing to participate in the study

METHODS

A written and informed consent to be included in the study was obtained in the patient's own language. A proforma was prepared for each patient and all their details were recorded in the same.

A detailed history regarding the complaint, duration, and associated factors were elicited. History regarding risk factors including immunocompromised status like diabetes (control/ DKA), HIV, drug intake etc, previous antibiotic therapy was elicited in detail with leading questions and their previous records if present. Other significant histories were also elicited and recorded.

Based on the duration of illness patients were classified into acute fulminant invasive (<4 weeks) and chronic invasive (>4 weeks).

After getting consent, the patients were examined. General and local examination was done. Examination of the nasal cavity, oral cavity, orbit, and cranial nerves was done in detail and recorded on admission and at regular intervals.

All patients were subjected to routine investigations of complete hemogram, renal function test, liver function test, urine routine, HIV and HBsAg, X-ray chest and ECG. Diabetic patients were evaluated with fasting and post-prandial blood glucose and urine acetone. Diagnostic nasal endoscopy was done for all patients and the findings were recorded. Either swab taken for KOH smear or sample tissue was taken for histopathological examination. This was used as confirmatory evidence with regards to the diagnosis of mucormycosis. Only these patients were included in the study. Radiological investigation included a compulsory Computer Tomography of paranasal sinuses and optional Computer Tomography of Brain and Magnetic Resonance Imaging of Brain. Other investigations were done as per the patient's requirement. All the investigations were recorded in the proforma.

The patients were staged based on the clinical extension of the disease. Rhino-maxillary mucormycosis includes disease involving the maxilla, oral cavity- palate, retro maxillary space, pterygopalatine fossa and the infratemporal fossa. Rhino-Orbital mucormycosis included patients with disease involving the Orbital (intraconal, extraconal)

lesion, preseptal cellulitis, Orbital cellulitis extending up to the orbital apex with or without the involvement of maxilla. Rhino-orbito-cerebral mucormycosis included patients with involvement of the cavernous sinus and the intracranial region with or without the involvement of the orbit and maxilla.

Management was tailored for each patient. Medical management includes strict glycaemic control, correction of metabolic factors, control/reversal of immunocompromised factors like neutropenia, correction of renal parameters, correction of anaemia as and when required and the antifungal agents. Expert opinions from Diabetology, Nephrology, Ophthalmology, Neuro-ophthalmology, Neurology, Neurosurgery, Haematology, Dentistry, General Medicine, Mycology, Microbiology, Pathology, Plastic Surgery was obtained depending on the requirement of the patient.

Amphotericin B iv was the main drug used in this study. 1mg/kg body weight/day up to a maximum dose of 50mg/day was given with 5% dextrose over 4-6 hrs after initially hydrating the patient with 500ml Normal saline. Completion of the course of treatment was considered to be 2g iv or above. But depending on the patient's requirement, it was increased to even up to 3g iv. If there was renal impairment, either it was given after obtaining nephrology opinion for the same or Inj. Liposomal Amphotericin was given up to 3g iv.

Syrup. Posaconazole was given in selected patients, in the dosage of 200ml thrice a day along with fatty foods for a period of 6 weeks.

T. Itraconazole 200mg twice a day was given in selected patients, especially for patients with mixed fungal infection and continued up to 6 months. Close monitoring of the liver function test was done during the same.

Surgical procedures included endoscopic debridement, maxillectomy, orbital decompression with or without optic nerve decompression, sequestrectomy etc. Patients were also taken up for multiple procedures as and when required. The surgical procedures were done in either general anaesthesia or local anaesthesia. Since there is very little bleeding and decreased pain sensation, local anaesthesia was the preferred modality. Transnasal endoscopic debridement of all the necrotic material and unhealthy mucosa up to the point of presence of active bleeding or pain sensation was the main surgical modality. Maxillectomy was performed with an endoscope or sublabial approach or open approach using Weber Ferguson incision. It was either partial (medial maxillectomy, inferior maxillectomy or subtotal maxillectomy) or total maxillectomy. The defect created either by maxillectomy or a pre-existing oroantral fistula was covered by obturator of the appropriate size. They were immediate (up to 2 weeks), intermediate (2 weeks to 3 months) and permanent (after 3 months). Orbital

decompression was most commonly done endoscopically, by removing the lamina papyraceae, incising the orbital periosteum and draining the pus if present. Other surgeries were done as and when required.

Since mucormycosis is a very fatal disease, the outcome is determined as death or survival. But, comparison of other factors like complaints and diagnostic nasal endoscopy with the initial presentation are also used to evaluate the patient post-treatment.

All the patients were followed up to 6 months with reviews at 1 month, 3 months and 6 months during which diagnostic nasal endoscopy was done. If needed, a Computer Tomography of the Paranasal Sinus was also taken.

RESULTS AND ANALYSIS

50 patients were included in our study. Data were collected with regards to the demographic details, complaints and clinical features, immune status evaluation, radiological and histopathological investigations, and treatment administered. The same was analyzed and are presented here. All the variables in this study are expressed as mean of value ± standard deviation.

BASIC CHARACTERISTICS

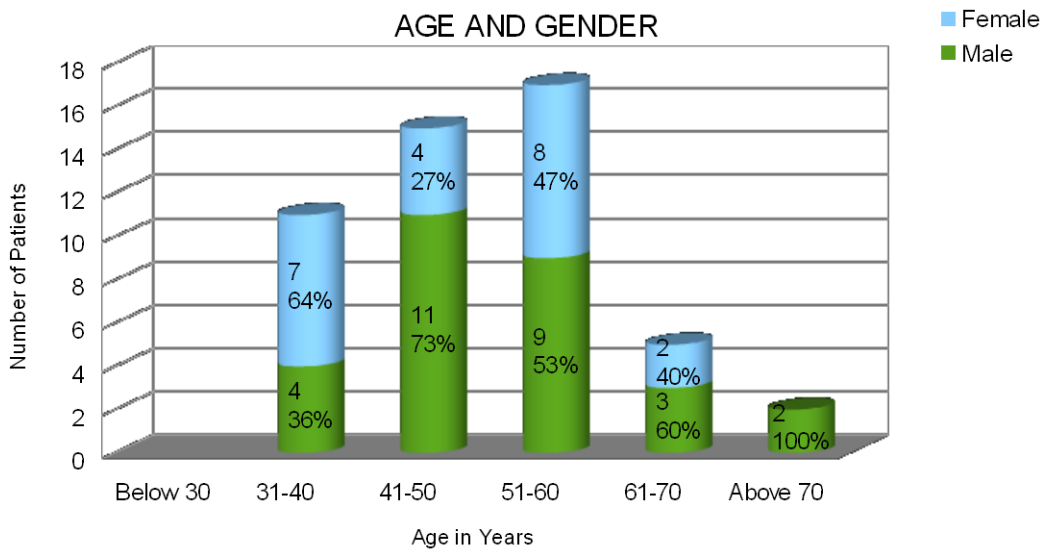


Fig 9: Age and Gender

AG E AND GENDER

Most of the patients were middle-aged, with 43/50 (94%) patients between the ages of 31-60 years. Mean age was 50.28 years ± 11.042 years. In gender distribution, there is a slight preponderance towards males with 29/50 (58%) male patients and 21/59 (42%) female patients.

DURATION OF ILLNESS

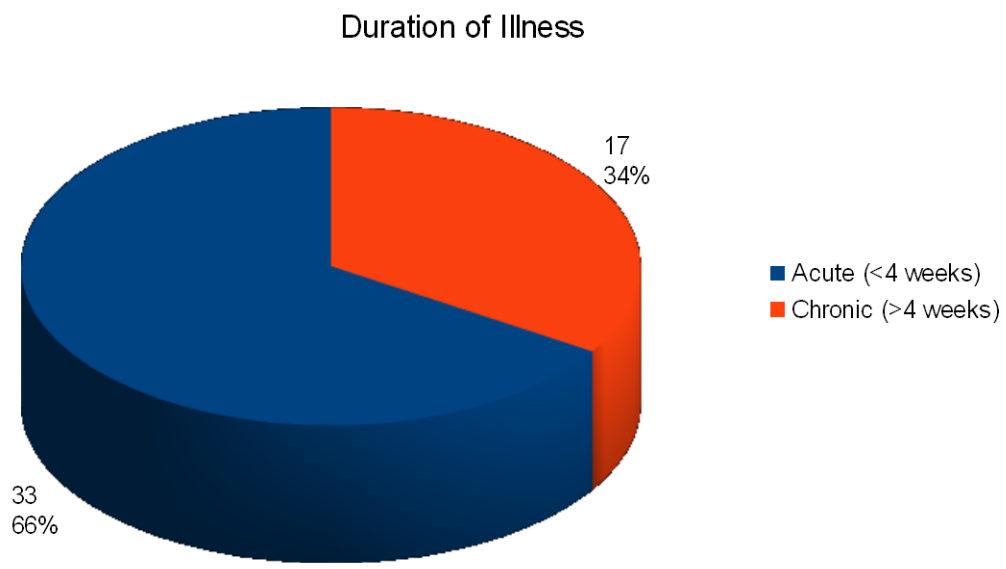


Fig 10: Duration of Illness

Most commonly, (66% - 33/50) the patients presented as acute fulminant invasive mucormycosis. These were the patients with typical features of blackish eschar and decreased sensation to touch. The patients presenting chronically (34% - 17/50), with duration of more than 4 weeks more commonly had atypical findings on diagnostic nasal endoscopy like polypoidal unhealthy mucosa rather than eschar. The mean duration of illness was 20.38 days ± 12.44 days. The mean duration to treatment initiation was 3.92 days, with treatment initiated in 29 patients within the first 3 days.

COMPLAINTS

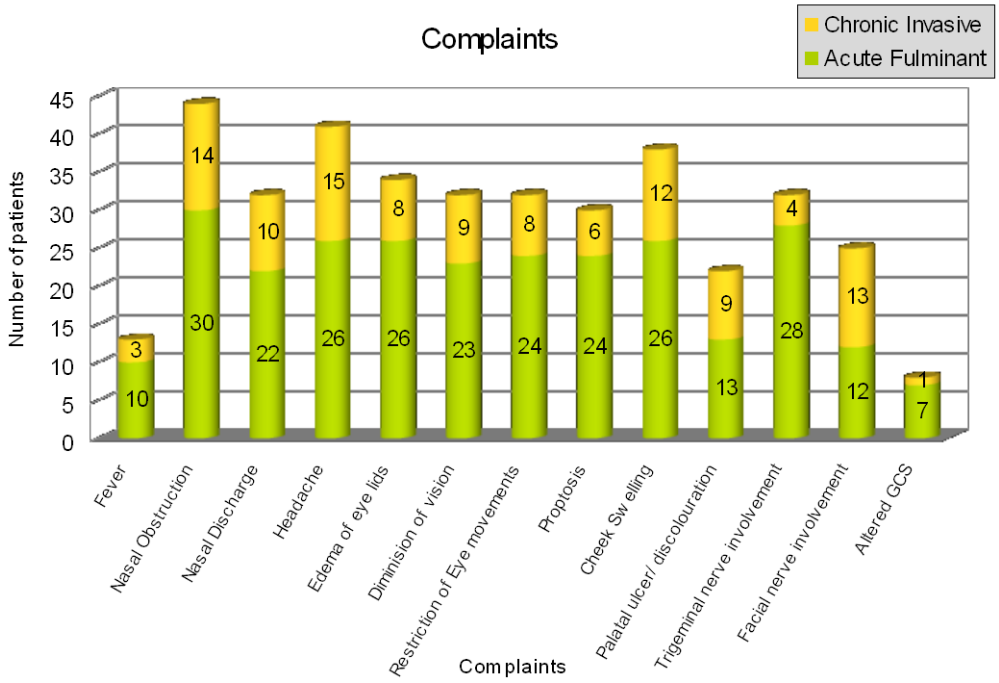


Fig 11: Complaints

Most common symptoms were Nasal obstruction (88%) (especially unilateral), and headache (82%) (more in the frontal region). Of the cranial nerves, trigeminal nerve (82%) was the most common nerve involved, manifesting as decreased sensation over the cheek, denoting the involvement of the maxillary branch. Many patients had this as their first presenting symptom. The facial nerve was involved in about one-third of the patients (32%) (most commonly House-Brackmann grade 3). In the eye, main symptoms were edema of the eyelids (68%), followed by a diminution of vision and restriction of eye movements (64%), and proptosis (60%). Presenting complaint as fever was variable and not common.

ASSOCIATED FACTORS

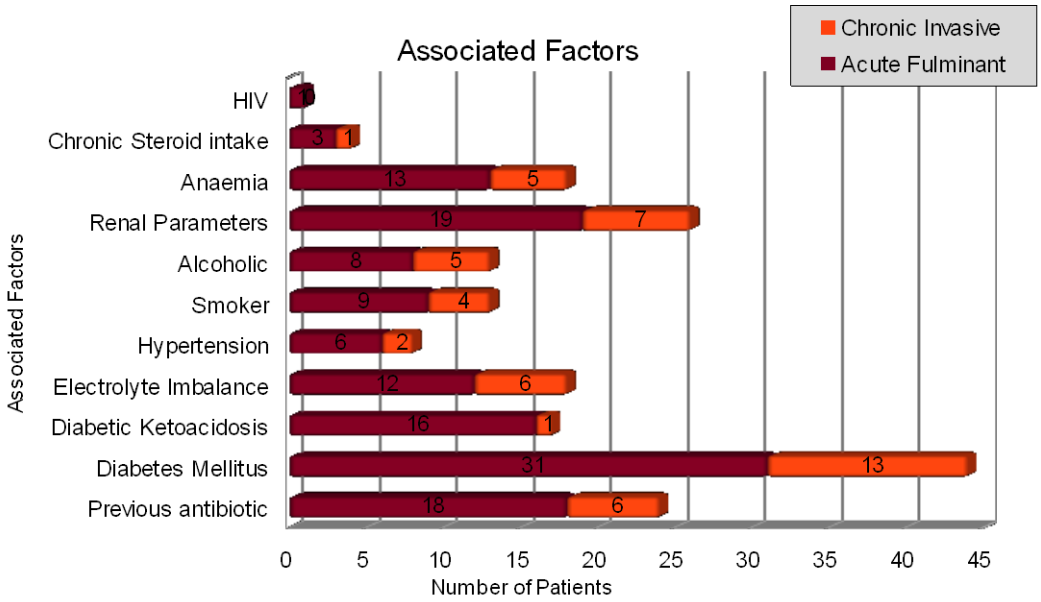


Fig 12: Associated Factors

As already known, Diabetes Mellitus (88%) was the most common factor associated with mucormycosis and patients with diabetic ketoacidosis presented with shorter duration of illness. Diabetes Mellitus is discussed in more detail in the next table. The next most common factor was previous antibiotic therapy (52%) which has been administered for various reasons, ranging from fever, chronic rhinosinusitis, chronic otitis media, to Fournier's gangrene, road traffic accident, elective surgery etc. Just about half the patients had deranged renal parameters (52%), manifesting as AKI or CKD or intermittent increase following Amphotericin B administration. But only 4 patients (i.e. only 17% of those with renal impairment) required dialysis. Electrolyte imbalance, most commonly hyponatremia or hypokalemia either due to abnormal renal function or diabetes, was another important factor associated in 36% of the patients. Anaemia (hemoglobin value of less than

10g%) was present in one-third of the patients, and half of those patients required a blood transfusion. Only one patient had HIV and 2 patients had HBsAg. There were 4 patients who were on chronic steroid therapy – 2 patients for SLE, one patient for Interstitial Nephritis and the 1 patient for rheumatoid arthritis.

GLYCEMIC CONTROL

Table-2: Glycemic Control

Diabetes	Number of Patients	Percentage
Duration		
Non-Diabetic	6	12%
Recently Diagnosed(<1year)	11	22%
1-5years	14	28%
5-10years	11	22%
>10 years	8	16%
Regular treatment	16/44	36% of diabetics
Under Control	7/44	16% of diabetics
Diabetic Ketoacidosis	17/44	39% of diabetics

As already mentioned, diabetes was the most common factor involved with mucormycosis. Only 6 patients were non-diabetic in this study. 11 of them had recent onset of Diabetes Mellitus. In 6 of these patients, mucormycosis was the presenting feature that led to investigating their glycemic status. Mean duration of diabetes mellitus was 5.52 years ± 5.544 years. With regards to the glycemic treatment, only 36% of these diabetic patients underwent a regular treatment of which not even half of the patients (44%) had their blood glucose level under control and diabetic ketoacidosis was present in 39% of the diabetic patient.

ENDOSCOPIC FINDINGS

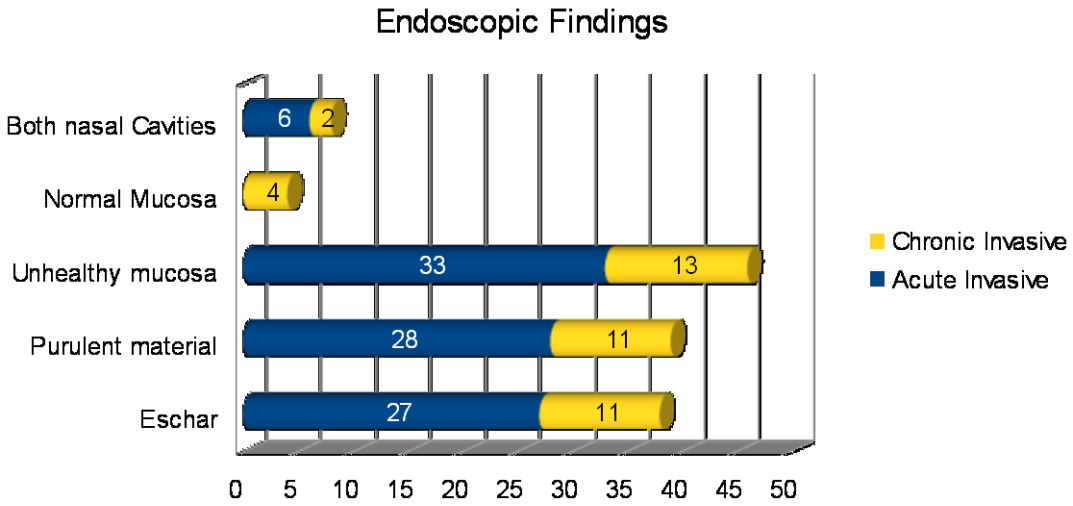


Fig-13: Endoscopic Findings

Endoscopic findings varied from typical blackish necrotic eschar (76%) to normal mucosa (8%). Unhealthy mucosa (92%) was the most common finding. This also had a varied presentation of pale mucosa, discoloured mucosa, inflamed mucosa, polypoidal mucosa, frank polyps etc with or without crusting. Hence, a high level of suspicion was needed. Purulent material (84%) mixed with crusts were quite common. Normal mucosa was present in 4 out of 17 cases of chronic invasive variant. Two main findings that were characteristic were the insensitivity to touch and the lack of significant fresh bleeding, both which helped both in diagnostic nasal endoscopy and in surgeries done under local anaesthesia. These could also be a tool for diagnosis as they were present in more than 90% of the cases.

RADIOLOGICAL FINDINGS

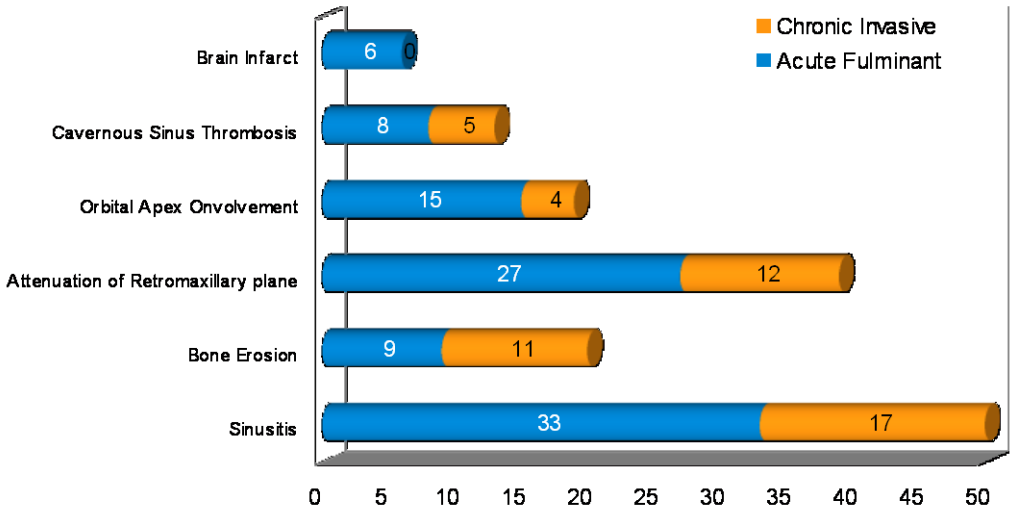


Fig-14: Radiological Findings - CT

In the CT, mucosal thickening in one or more of the sinuses was the most consistent finding present in all the cases. But it is extremely non-specific. Bone erosion occurred in 40% of the cases. But it was not present in the early stages. One consistent finding was the unilateral attenuation of retro-maxillary area with fat plane stranding with an intact posterior maxillary wall (78%). This was found to occur as very early in the disease process and is much more specific than bone erosion. Orbital involvement was present in 64% of the cases. Orbital apex syndrome and cavernous sinus thrombosis were present as the disease progressed from the nasal cavities towards the cranial cavity. Intracranial extension was present only in 14% of the patients and was in the form of an infarct in most of the patients and a space-occupying lesion in one patient.

MICROBIOLOGY

In most of the cases (84%), there was exclusively Mucorales. But in about 16% there was a mixed fungal infection where Mucorales was the predominant pathogen.

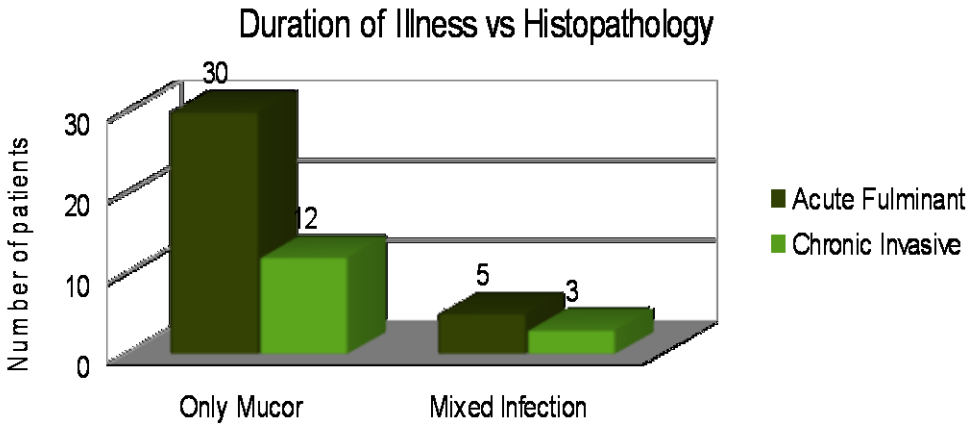


Fig-15: Duration of Illness Vs Histopathology

There was not much difference in the proportion of cases caused by only mucor or mixed fungal infections when compared with the duration of illness.

STAGE

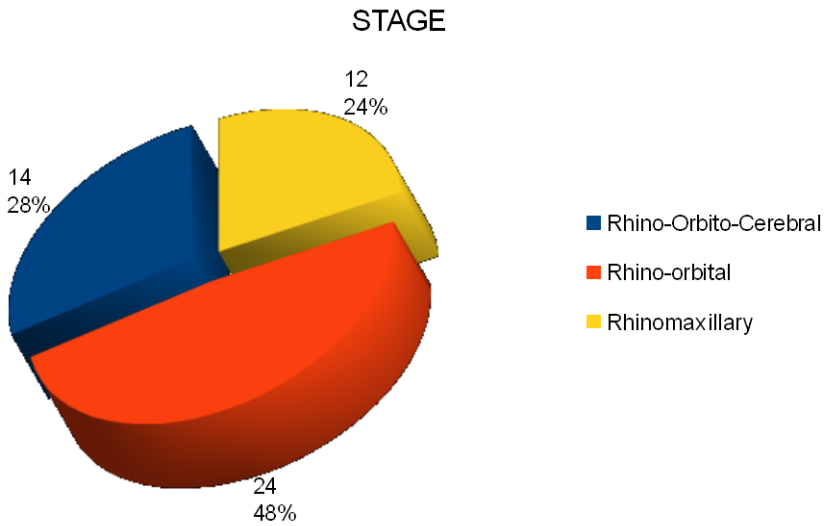


Fig 16: Stage of Presentation

Most of the patients presented with Rhino-orbital mucormycosis (48%). The rhino-maxillary mucormycosis(28%) presented as a more chronic course and extends towards the cheek, palate, retro-maxillary space, pterygopalatine fossa and the infratemporal fossa. But the rhino-orbital mucormycosis extended faster into the cavernous sinus which, in turn, extended into the brain casing infarct.

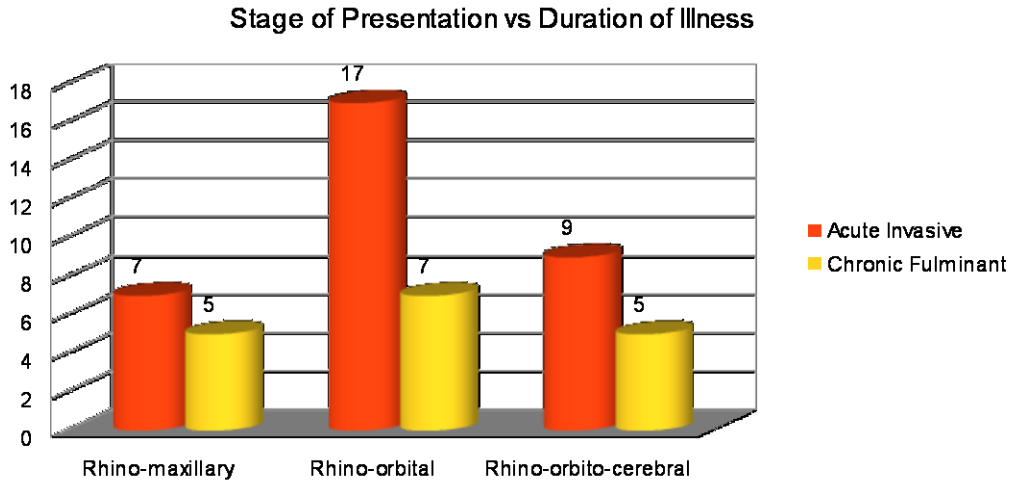


Fig-17: Stage of Presentation Vs Duration of Illness

In all stages, acute invasive presentation was more common. Rhino-orbital was the most common presentation of acute invasive type.

ANTIFUNGAL

Table 3: Antifungal

Antifungal	Number of Patients	Percentage
Inj. Amphotericin B	47	94%
Completed Treatment	37	74%
Incomplete Treatment	10	20%
Inj. Liposomal Amphotericin	4	8%
T. Itraconazole	7	14%
Syp. Posaconazole	6	12%

Amphotericin B iv was the main antifungal agent used. During the course of this drug, renal parameters, potassium and electrolyte levels were closely monitored. Except for 3 patients, it was given for all other patients. Few patients had an interrupted course due to reasons like elevated renal parameters or hypokalemia. There were no major reactions to Amphotericin B. 1 patient developed chills after a dose of Amphotericin B that was controlled with Inj. Avil 2cc im. One patient had severely elevated renal parameters needing dialysis and hence was given Liposomal Amphotericin in the place of Amphotericin B. 9 other could not complete the course of 2g or more due to discharge against medical reasons (4) or death (5). T. Itraconazole 200mg 1-0-1 was given for 7 patients with monthly monitoring of liver function test.

SURGICAL MANAGEMENT

Table 4: Surgical Management

Surgical Management	Number of Patients	Percentage
Endoscopic Debridement	46	92%
Maxillectomy	15	30%
Orbital Decompression	20	40%
Sequestrectomy	3	6%

The surgeries were done under local or general anaesthesia. Most common procedure done was Endoscopic debridement (92%). It was done multiple times so as to repeatedly remove the necrotic debris. Maxillectomy was done in 15 patients. 2 patients underwent Open

maxillectomy with Weber Fergusson incision. 7 patients underwent partial infrastructure maxillectomy with sublabial incision. 3 patients underwent total maxillectomy with sublabial incision. 3 patients underwent endoscopic medial maxillectomy. Obturator (immediate, intermediate and permanent) was given as and when required. Orbital decompression with or without optic nerve decompression was done in 40%. 1 patient underwent subtemporal excision of Lesion in Cavernous Sinus Thrombosis the histopathological report of which turned out to be mucormycosis. 1 patient underwent flap reconstruction of the cheek due to skin necrosis.

NUMBER OF SURGICAL PROCEDURES

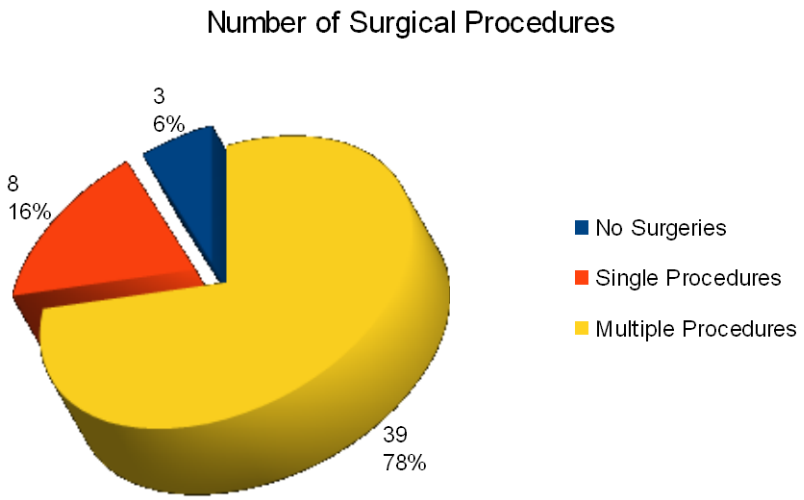


Fig 18: *Number of Surgical Procedures*

3 patients did not undergo any surgery and all 3 of them died.

8 patients underwent only single surgery. 2 of which died within the first week.

Multiple surgeries were done in most of the patients 78%. On an average 3 surgeries were done for each patient. Multiple surgeries were required for removing the fungal debris repeatedly and it was done as and when required.

42 patients underwent at least one surgery under local anaesthesia. The advantage of which was lack of sensation and lack of bleeding. 27 of these patients were managed completely under local anaesthesia with no proceedure done in general anaesthesia. Only 15 patients required general anaesthesia.

OUTCOME

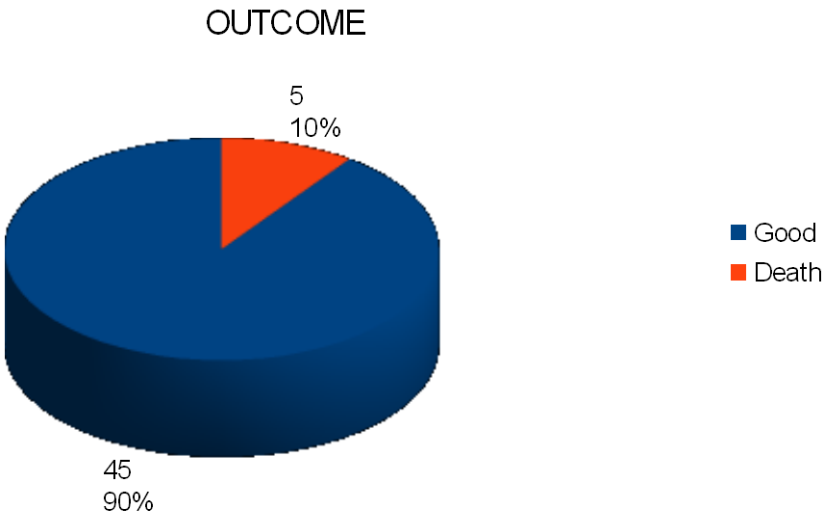


Fig 19: Outcome of the disease

Since the mortality rate of mucormycosis is very high (>50%), the outcome was measured with mortality and survival rates. In this study, there was a 90% survival rate at the time of discharge. Only 10 % mortality was present.

FOLLOW UP

Of the 45 surviving patients, 2 patients died before 6 months but none were due to mucormycosis and 4 were lost to follow up. 36 were followed up for 6 months or more and were free of disease. 3 patients were followed up till 4 months and were free of disease. 2 patients developed nasal myiasis 1 year later. They both had necrotic tissue in their nasal cavities and were managed by debridement and removal of the myiasis without antifungal therapy. Both did well 6 months later.

STATISTICS

The statistics were done using the software – Statistical Package for Social Sciences (SPSS) version 17. The statistic tests that were used are descriptive and chi-square tests.

The age and sex of the patients statistically had no correlation with the duration of illness or stage the disease or outcome of the patients.

Of the complaints, Altered GCS (Glasgow Coma Scale) was the only variable which when compared with outcome was statistically significant (p-value-0.000).

Duration of illness was not influenced by the presence of diabetes. But the presence of diabetic ketoacidosis significantly influenced the duration of illness (p-value 0.004) showing that the patients with DKA presented earlier.

Table 5: Stage of presentation with Uncontrolled Diabetes, Diabetic Ketoacidosis, and Electrolyte Imbalance

Variable		Stage			Total	Statistics (p-value)
		RM	ROM	ROCM		
Uncontrolled Diabetes	Present	6(12%)	20(40%)	11(22%)	37(74%)	0.003
	Absent	6(12%)	4(8%)	3(6%)	13(26%)	
Total		12(42%)	24(48%)	14(28%)	50(100%)	
Diabetic Ketoacidosis	Present	0	7(14%)	9(18%)	16(32%)	0.002
	Absent	12(24%)	17(34%)	5(10%)	34(68%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	
Electrolyte Imbalance	Present	2(4%)	7(14%)	9(18%)	18(36%)	0.026
	Absent	10(20%)	17(34%)	5(10%)	32(64%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	

The presence of diabetes or the duration of diabetes per-se was not a statistically significant risk factor. But both the control of diabetes (p-value 0.003) and the presence of Diabetic ketoacidosis (p-value 0.002), along with electrolyte imbalance (p-value 0.026) statistically correlated with the stage of the disease which in turn shows that an acidotic state aids in the spread of infection.

Table 6: Outcome of the disease with Uncontrolled Diabetes, Diabetic Ketoacidosis, and Electrolyte Imbalance

Variable		Outcome		Total	Statistics (p-value)
		Good	Death		
Uncontrolled Diabetes	Present	32(64%)	5(10%)	37(74%)	0.342
	Absent	13(26%)	0	13(26%)	
Total		45(90%)	5(10%)	50(100%)	
Diabetic Ketoacidosis	Present	11(22%)	5(10%)	16(32%)	0.001
	Absent	34(68%)	0	34(68%)	
Total		45(90%)	5(10%)	50(100%)	
Electrolyte Imbalance	Present	13(26%)	5(10%)	18(36%)	0.002
	Absent	32(64%)	0	32(64%)	
Total		45(90%)	5(10%)	50(100%)	
DKA & Electrolyte Imbalance	Present	7(14%)	5(10%)	12(24%)	0.000
	Absent	38(76%)	0	38(76%)	
Total		45(90%)	5(10%)	50(100%)	

The outcome did not correlate well with the control of the diabetes mellitus at the time of presentation probably due to the improvement of glycemic status during the course of the illness. But both diabetic ketoacidosis (p-value 0.001) and electrolyte imbalance (p-value 0.002) separately and together (p-value 0.000) were statistically significant factors with respect to the outcome of the disease. The outcomes were also dependent on the severity and reversibility of diabetic ketoacidosis and electrolyte imbalance.

Table 7: Stage of presentation with radiological findings

Variable		Stage			Total	Statistics (p-value)
		RM	ROM	ROCM		
Retro-maxillary fat plane stranding	Present	9(18%)	17(34%)	13(26%)	39(78%)	0.002
	Absent	3(6%)	7(14%)	1(2%)	11(22%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	
Orbital Apex Involvement	Present	0	7(14%)	12(24%)	19(38%)	0.000
	Absent	12(24%)	17(34%)	2(4%)	31(62%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	
Cavernous Sinus Thrombosis	Present	0	1(2%)	13(26%)	14(28%)	0.000
	Absent	12(24%)	23(46%)	1(2%)	36(72%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	
Involvement of Brain	Present	0	1(2%)	6(12%)	7(14%)	0.001
	Absent	12	23	8(16%)	43(86%)	
Total		12(24%)	24(48%)	14(28%)	50(100%)	

Table 8: Outcome of disease with Radiological findings

Variable		Outcome		Total	Statistics (p-value)
		Good	Death		
Retro-maxillary fat plane stranding	Present	35(70%)	4(8%)	39(78%)	0.909
	Absent	10(20%)	1(2%)	11(22%)	
Total		45(90%)	5(10%)	50(100%)	
Orbital Apex Involvement	Present	15(30%)	4(8%)	19(38%)	0.041
	Absent	30(60%)	1(2%)	31(62%)	
Total		45(90%)	5(10%)	50(100%)	
Cavernous Sinus Thrombosis	Present	10(20%)	4(8%)	14(28%)	0.006
	Absent	35(70%)	1(2%)	36(72%)	
Total		45(90%)	5(10%)	50(100%)	
Involvement of Brain	Present	3(6%)	4(8%)	7(14%)	0.000
	Absent	42(84%)	1(2%)	43(86%)	
Total		45(90%)	5(10%)	50(100%)	

Radiological features correlated well with the stage and outcome of the disease. The more advanced stage of the disease, presented with more involvement of the structures on radiology and prognosis was worse.The duration of illness was a statistically significant factor with regards to bone erosion (p-value 0.028) proving that it is not present in the early stages.

Table 9: Outcome of disease with Stage of presentation

Variable	Outcome			Total	Statistics (p-value)
	Good	Death	Survival Rate		
RM	12(24%)	0	100%	12(24%)	0.022
ROM	23(46%)	1(2%)	96%	24(48%)	
ROCM	10(20%)	4(8%)	71%	14(28%)	
Total	45(90%)	5(10%)	90%	50(100%)	

The stage of the disease directly correlated with the outcome of the patients with no deaths in the rhino-maxillary stage of mucormycosis, 1 death in the Rhino-orbital stage of mucormycosis and 4 deaths in the rhino-orbito-cerebral stage of mucormycosis. Hence, it shows that intracranial extension is a grave sign with regards to the survival of the patients.

Table 10: Outcome with Treatment Modalities

Variable		Outcome		Total	Statistics (p-value)
		Good	Death		
Number of Surgeries	No Surgery	0	3(6%)	3(6%)	0.000
	Single	6(12%)	2(4%)	8(16%)	
	Multiple	39(78%)	0	39(78%)	
Total		45(90%)	5(10%)	50(100%)	
Antifungal Agents	Completed	40(80%)	0	40(80%)	0.000
	Incomplete	5(10%)	5(10%)	10(20%)	
Total		45(90%)	5(10%)	50(100%)	

The outcome was statistically significant when compared to the treatment modalities like multiple surgeries and antifungal therapy. This proves multiple surgeries have a better outcome than single or no surgeries and completion of antifungal agents has a significant role in the survival of the patients.

DISCUSSION

In 1815, Meyer, recognized the pathogenicity of mucormycosis when he found the Phcomycetes. The first well-documented case of human infection of Mucor described by Boke in. Patlauf in 1885, decribed the first case of Isolated cerebral mucormycosis in human beings. The first cure was reported by Harris in 1955. In 1953, the first antifungal agent, Amphotericin-B, obtained from Streptomyces Nodosus, was discovered.. In 1958, it was used for a case of sinonasal mucormycosis by Smith and Kirschen.[23] The term 'zygomycosis' was defined as any invasive fungal infection that was caused by the species of the phylum Zygomycota by Ajello et al in 1976.[41] This term was replaced by Baker to 'mucormycosis'.[23]

Mucormycosis is an uncommon infection, occuring 10-fold and 50-fold less frequently, compared to invasive aspergillosis or candidiasis.[42] It comprises of 8.3%–13% of all fungal infections encountered at autopsy.[43] The prevalence of mucormycosis in India is 0.14 cases per 1000 population, which is approximately 70 times the worldwide-estimated rate. It ranges between 208 177 and 137 807 cases with a mean of 65 500 (38.2%) deaths per year due to the same.[44]

Over the last decade, as shown in several studies, there has been a dramatic increase in the incidence of invasive fungal infections. This is

probably due to an increase in the size of the population at risk and increased awareness. In developed countries hematological malignancies and stem cell transplantion may be the cause. However, in India, an alarmingly higher (73.6%) association was present between uncontrolled diabetes mellitus and invasive zygomycosis. In the study by Chakrabarti et al, 129 cases (12.9 cases/year) were diagnosed during 1990-1999 compared to 178 cases (35.6 cases/year) during 2000-2004 from the same center.[45] Whereas, the overall prognosis has increased drastically from 100% mortality before the 1960s to around 40% at present.[46]

GEOGRAPHIC

In the study by Jeong et al[7], of 851 cases, 290 were from Europe (34%), 267 from Asia (31%) and 239 from North or South America (28%). Whereas, in most other studies, like Mignonga et al[14], India had the highest incidence of mucormycosis(44.3%) followed by USA(19.8%) and Australia(5.7%). The reason for the highest incidence in India may probably be due to environmental factors, malnourishment, low socio-economic status, scarce hygienic conditions, etc. But the most important reason is diabetes mellitus, which is rampant in India.[14]

SEASONAL

Seasonal variations of mucormycosis may be due to the variations in the temperature, humidity, and rainfall. Petrikkos observed August and September as the most common months in his study. Environmental

factors India provides an optimum set-up for these fungi and these may contribute to the disease prevalence.[44]

Bartzokas who studied the mycological flora in the air in Greece found that Mucor species were cultured only from June to December with a peak concentration in August. Similarly, in India, the concentration of air fungal spores increases during the transition from summer to the rainy season. The moisture levels in soil increases, quickening the decay of plant debris. This when disturbed during plowing, releases the fungal spores into the air. Babu et al concluded that the agricultural practices correlated with the peak incidence incidence of mucormycosis.[47]

In our study also this correlated with the peak incidence between mid-June to September for all the Farmers. But, in other patients, especially females, the peak incidence was in February and March. The reason for this is not known.

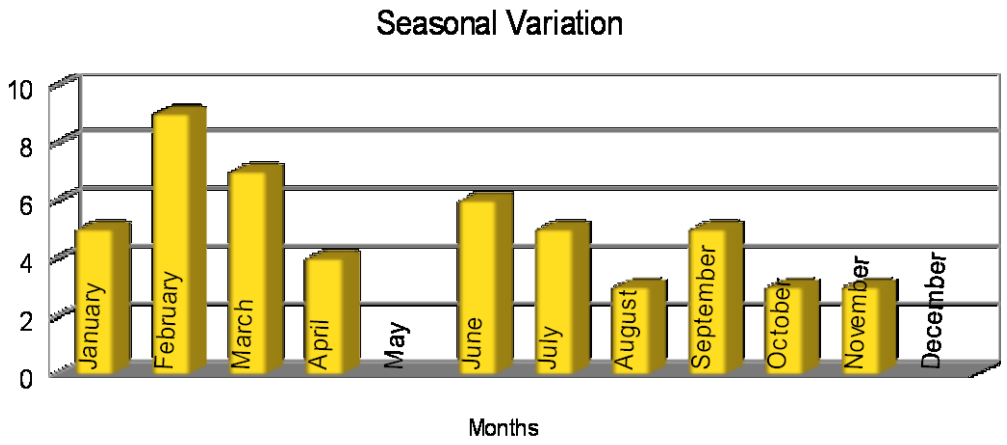


Fig-20: Seasonal Variation

AGE AND GENDER

Majority of the patients were in their middle adulthood in most studies, with few cases in the extremes of age. Similarly in our study, the majority of the cases were between 40 and 60 years, with decrease in extremes of age. Mean age was 50.28 years ± 11.042 years.

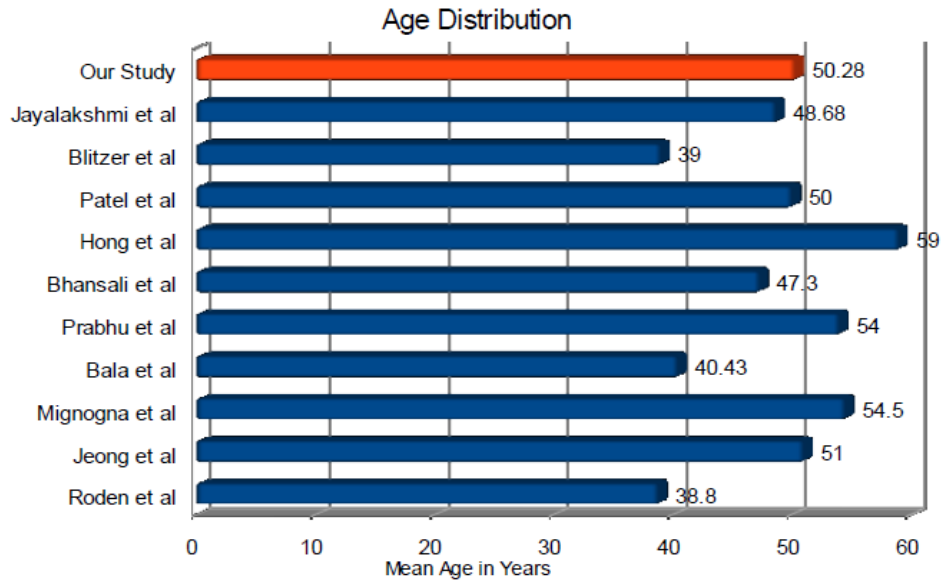


Fig-21: Age Distribution

Mucormycosis is uncommon in children and the features are not similar. In the paediatric epidemiological study of 63 patients by Pana et al, disseminated form (38%) was the most common type. Also, hematological malignancy (46%) was their most common underlying condition with diabetes present only in 4.8%.

Since in our center mainly more than 12 years were only treated, no pediatric patients were present in our study.

In most of the studies, there was a male predominance. The reason is not known. Our study also showed a similar feature of 58% male patients.

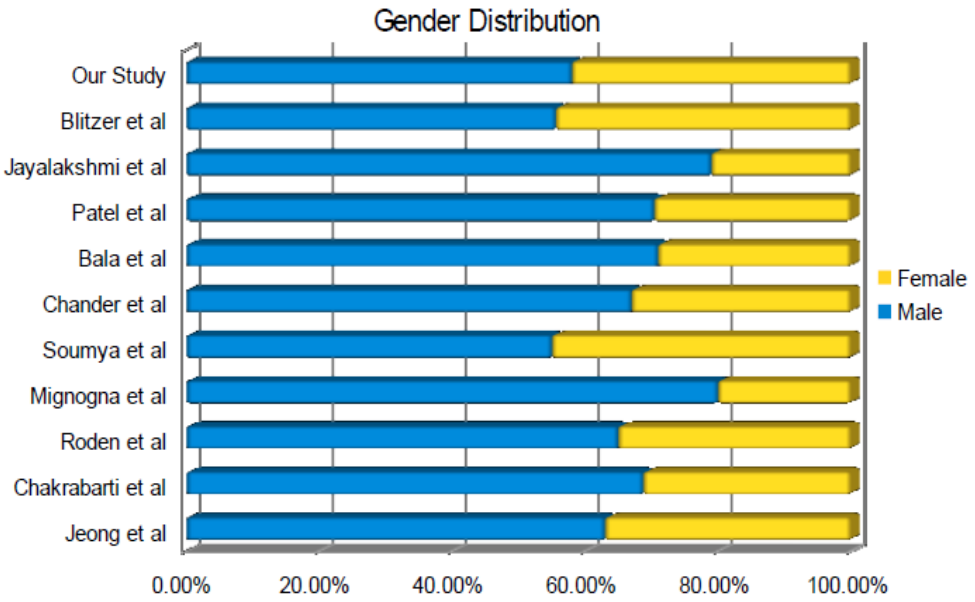


Fig-22: Gender Distribution

TYPE

Mucor can affect several parts of the body. It can be classified as Rhino-orbito-cerebral, Disseminated, Pulmonary, Gastrointestinal, cutaneous, etc. Rhino-cerebral mucormycosis is the most common type of mucormycosis, it accounts for one-third to one-half of the cases of mucormycosis in most of the studies.

Table-11: Sites of Mucormycosis

	Chakrabarti et al - India (178 patients)	**Roden et al (929 patients)**	**Jeong et al (851 patients)**
ROCM	58%	39%	34%
Pulmonary	6%	24%	20%
Cutaneous	14%	19%	22%
Disseminated	7%	23%	13%

The duration of symptoms to diagnosis was shorter in patients with ROCM 12days and cutaneous mucormycosis 11days, compared to involvement of deep organs 22days.[49] This reason is the early presentation, accessibility and easier examination of these regions.

RISK FACTORS

There are several risk factors are present including - Uncontrolled Diabetes Mellitus, hematological malignancy, solid organ and bone marrow transplantation, immunocompromised status, neutropenia, chronic steroid usage, trauma, metabolic acidosis, previous fungal prophylaxis, extensive antibiotic therapy, aluminum and iron overload, deferoxamine therapy, illicit intravenous drug use, malnourishment, neonatal prematurity, nosocomial spread etc.[43]

The more normal the immune system, the slower the progression of the disease and the more elusive the diagnosis, until it declares itself with significant symptoms prompting appropriate biopsies or cultures.[30]

Uncontrolled diabetes mellitus was the commonest risk factor in most studies. In nearly 40% of the patients mucormycosis may be the first manifestation of diabetes mellitus.[49] It is rarely seen in those with metabolically controlled diabetes.[43]

In the study of 929 patients by Roden et al, diabetes mellitus was the most common underlying condition 36% (337/929). Only 68

patients(20%) were type 1, of which 48% had DKA. In type 2 DM, 34% had DKA. The second largest group had no primary underlying disease. The next largest group was patients with underlying malignancies, 95% of which was hematological malignancies.

Each site of mucormycosis had a specific risk factor, even though no reason has found. In ROCM 66% of the patients had DM.[6]

Table-12: Underlying Conditions

Underlying condition	Most Common type of Mucormycosis
Diabetes	ROCM
Malignancy and bone marrow transplant recipient	Pulmonary 2nd ROCM
No underlying condition	Cutaneous
Deferoxamine	Disseminated
Solid Organ transplantation	Both Pulmonary and ROCM
Infections in IDUs	Cerebral mucormycosis.

Roden et al also observed that in the past 20 years, every year there is an increase in the incidence of mucormycosis in patients with diabetes mellitus and in the more classically defined immunocompromised risk groups.[6]

Jeong et al[7] observed diabetes mellitus (40%) to be the most common factor 20% of which had DKA. Especially in African or Asian countries, this was the most common factor. Also, ROCM most

commonly was present in patients with diabetes (53%) than without (23%). Of 32% hematological malignancies Acute Myeloid Leukemia was the most common (62%) and renal transplant(58%) was the most common Solid organ transplantation (14%). Corticosteroid abuse was present in 33% while major/minor trauma was present in 20% of the patients.

Yohai et al[50] DM was present in 60% with 30% DKA. Renal problems including chronic renal insufficiency and kidney transplantation were present in 19%. Deferoxamine therapy (6.2%) and Leukemia (5.5%) were the least contributing factor in their study. Other causes of metabolic acidosis like trauma, severe burns, dehydration, malignancy etc were also important associated factor.

Of 179 patients Blitzer et al found that DM was present in 70% and 23% had some other underlying diseases like leukemia, renal disease, transplantation, diarrhoea, steroids use etc. Only 4.4% had no underlying disease.

In the study by Hong et al, 98% had an underlying disease (63/64), commonest of which was DM (67%), followed by hematological malignancy (22%) and solid cancer (19%).

Chakrabarti et al[45] in his study, concluded, uncontrolled DM (73.6%) as the most significant risk factor in all types. 56 of the those

131 patients were diagnosed as having DM for the first time. 75 patients were type 2 and 10 were type 1 DM.

Similar to most other studies, in our study, diabetes mellitus was the most common underlying condition - 44/50(88%) patients. 11 were recently diagnosed and 6 had mucormycosis as the presenting feature. Of the 44 diabetics, only 16 underwent regular treatment. In spite of that, only 7/44 patients had a good glycemic control. 17 patients had DKA proven with urine acetone testing.

In our study, the control of diabetes strongly correlated with the stage of presentation (p-value 0.003). Comparison of DKA with the stage (p-value0.002) and the outcome (p-value 0.001) was also statistically significant. Similarly, the electrolyte imbalance also correlated statistically with the stage (p-value 0.026) and outcome (p-value 0.000). In addition, the combination of both DKA and electrolyte imbalance was related to the advanced stage of the disease and worse prognosis. This proves that rather than the presence or duration of the diabetes mellitus, the glycemic control at that point in time was more important. Adequate glycemic control and metabolic control, thus reversing the underlying condition is one of the prime principles of the treatment strategy.

Diabetes and ketoacidosis render the phagocytic cells dysfunctional due to impaired chemotaxis and defective killing via both oxidative and

non-oxidative pathways. DKA patients have an acidic serum pH due to which free iron levels are elevated. These are a major nutrient element and govern susceptibility to Mucorales. Thirdly, due to the elevated levels of iron and glucose, an increase in the expression of Cot H3 protein (spore coat protein homologson *Mucorales*) and GRP-78, (a glucose-regulated protein belonging to the HSP-70 family) is present. A fraction of GRP-78 is translocated to the cell surface in some cells, where it acts as a receptor mediating the penetration and damage of endothelial cells by Mucorales, leading to the observed angioinvasion.[44]

Renal parameters were deranged in 24 patients. Even though it did not statistically correlate with the stage or outcome, it plays an important role in metabolic correction and administration of Amphotericin B. 16 patients had increase in their creatinine levels which returned to their baseline after Amphotericin B was discontinued. Of that only 4 patients required hemodialysis. In one patient alone, Amphotericin B had to be discontinued and Liposomal Amphotericin was administered instead.

Anaemia was present in 17 patients. But it was also statistically not related to the stage of presentation or outcome of the disease. None of our patients had any underlying malignancies or organ transplantation, even though these are major risk factors in several studies. The reason for this may be due to the distribution of patients in our center.

Chronic corticosteroid-based therapy enhances a patient's susceptibility to mucormycosis causing qualitative defects in neutrophils and macrophages. It may also have a role in steroid-induced diabetes.[43]

4 patients in our study were on chronic steroid therapy - 2 for SLE, 1 for interstitial nephritis and 1 for rheumatoid arthritis. In all these patients steroids were temporarily withdrawn. These patients responded well. One patient alone died a few months later due to pulmonary complications of SLE.

Nosocomial mucormycosis may occur due to exposure to heavy air fungal loads like contaminated air filters, construction work, etc or through iatrogenic transmission like tongue depressors, contaminated wound dressings, intravenous catheters, transdermal nitrate patches etc.[43]

In our study, 26 patients had received previous antibiotic therapy for varied periods for various reasons like fever, dental extraction, previous chronic rhinosinusitis, chronic otitis media, typhoid, Fournier's gangrene, road traffic accident, elective surgery, glycemic control with 4 patients taking over the counter pills. 6 patients already were admitted in the hospital when their symptoms started. This factor has not been discussed in previous literature. Further analysis regarding the class of antibiotics, duration and their correlation to the development

mucormycosis needs to be studied to conclude if this is a significant factor.

HIV produces a defect in the T helper cells. T cell depletion is not a major determinant in the development of mucormycosis.[45]

Similarly, in our study, only one patient was HIV positive. But even that patient had additional DM with DKA. Hence, HIV may not necessarily the reason for immunocompromise in that patient as well.

COMPLAINTS AND CLINICAL FEATURES

ROCM is known to exist in two forms - the well-known acute fulminant form and the recognized chronic form".[51]

The time between onset of symptoms and diagnosis was usually around 10-15 days. The median duration of illness before presenting to the hospital was 14 (1-91) days in Patel's study,10-50days in Zhao's study[52], and 12 hours to 1 week in Shah's study. Also in Shah's study, the mean time from diagnosis to death was 4 days.[22] In our study, the mean duration of illness at presentation was 20.38 days ± 12.44 days.

Depending on the extent of disease clinically, it is classified into 3 stages -

Stage 1 - Rhino-maxillary mucormycosis

Stage 2 - Rhino-orbital mucormycosis

Stage 3 - Rhino-orbito-cerebral mucormycosis

The initial symptoms may be extremely subtle and non-specific making it extremely difficult to differentiate from sinusitis. There may be difficulty in differentiating it with acute bacterial orbital cellulitis.

In the Rhino-maxillary stage, nasal obstruction, nasal discharge and headache, were the most common symptoms. Other early symptoms were facial pain and parasthesia. Fever was variable. Soft tissue swelling of the face and palatal ulceration also developed.

A - 3x2 cm erosion in the right half of the hard palate
B - 2x1 cm erosion of the left half if the palate with surrounding mucosal discolouration
C - Right cheek swelling with minimal left orbital cellulites
D - Left Orbital cellulitis with swelling of the Left cheek and necrosis of the skin over the cheek

In the rhino-orbital stage, symptoms were eyelid edema, conjunctival suffusion, proptosis, ophthalmoplegia, blurry vision, orbital cellulitis etc. With intracranial spread in the rhino-orbito-cerebral stage, other symptoms appear. Early manifestations of cavernous sinus thrombosis are ophthalmoplegia and diplopia. These were observed radiological changes.[42] Signs and symptoms in the contralateral eye (bilateral ophthalmoplegia, proptosis, chemosis, vision loss) is also an ominous sign suggesting the development of cavernous sinus thrombosis.[48] Altered sensorium, hemiplegia or loss of consciousness may lead to rapid death.

Multiple cranial nerves were involved – olfactory, optic, occulomotor, trochlear, trigeminal (maxillary branch), abducens and facial nerve. Complete recovery rarely occurs even after successful treatment of the patient.

Table-13: Symptoms

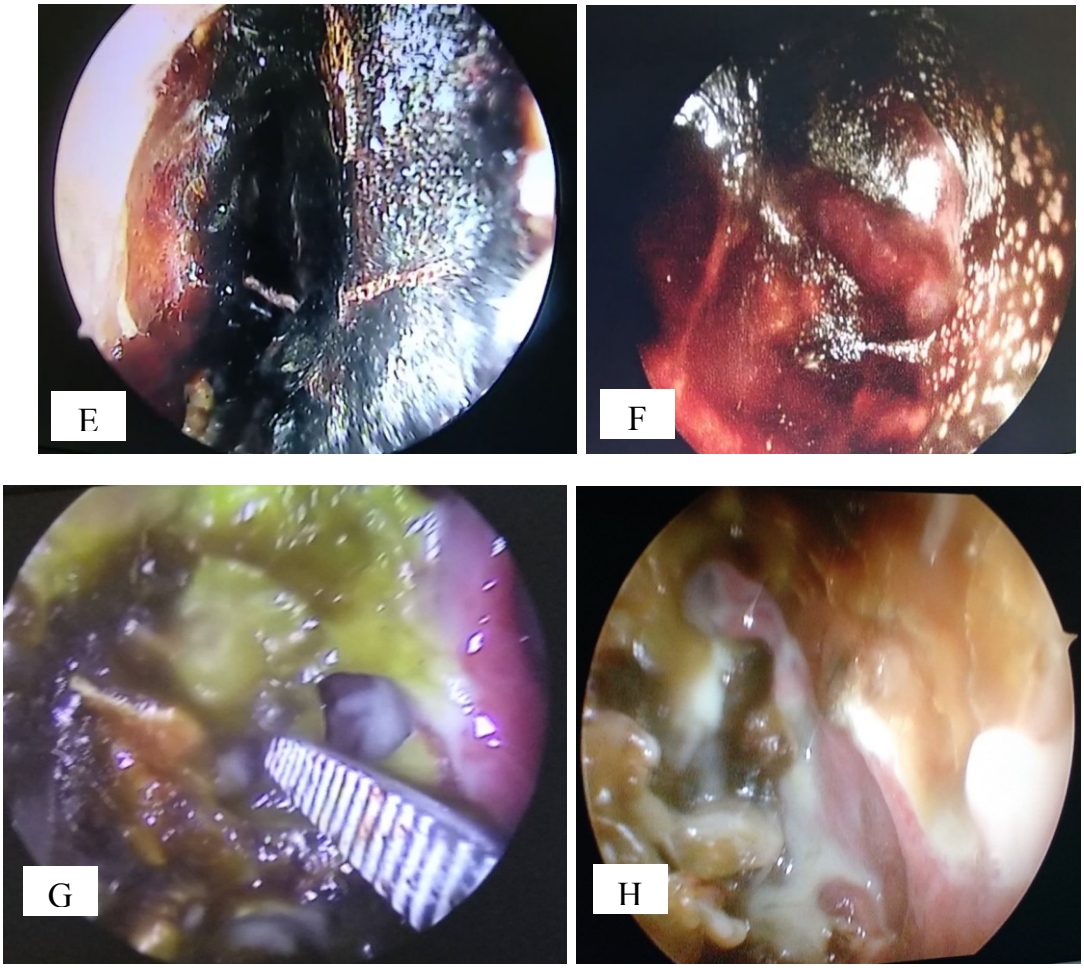
Symptoms	Chakrabarti et al	Zhao et al	Yohai et al	Our Study
Fever	44%	81.8%	44%	36.4%
Nasal Obstruction	36%	54.5%	17%	88%
Nasal Discharge	19%	45.5%	18%	6%
Headache	39%	63.6%	25%	82%
Periorbital swelling	42%	81.8%	34%	68%
Decreased Vision	61%	100%	30%	64%
Ophthalmoplegia	75%	100%	29%	64%
Proptosis	72%	81.8%	16%	60%
Cheek Swelling	31%	72.7%		76%
Palatal necrosis	25%	-	14%	44%
Facial numbness	14%	-	7%	80%
Facial palsy	6%	-	11%	32%
Altered consciousness	36%	54.5%		16%

Anaesthetic regions of the face or oral cavity precede the development of objective changes in the mucosa and are features of early invasive process.[33]

In early stages, the infected tissue appears normal. It progresses through an erythematous phase, with or without edema, then a violaceous appearance, and finally, of a black, necrotic eschar as the tissue infarction occurs.[48]

The most consistent physical finding is an alteration in the appearance of the nasal mucosa. Discoloration, granulation, and ulceration often replaced the normal pale-pink mucosa. They may be gray, green, white, or black. White discoloration indicates tissue ischemia secondary to an angiocentric invasion, whereas black discoloration, a late finding signifies tissue necrosis. In this series, mucosal abnormalities were seen most commonly on the middle turbinate (67% of patients), followed by the septum (24%), palate (19%), and inferior turbinate (10%).[5]

Similarly in our study, various appearance of the mucosa in the nasal cavity was present. Middle turbinate was the most common site of affliction.



E - Blackish eschar
F - Brownish eschar with fungal material
G - Brownish and greenish crusts with pus
H - Brownish crusts with pus and unhealthy mucosa

Meticulous physical examination including examination of oral cavity, eye, and cranial nerves is very important for diagnosing and assessing extent as the radiological findings are non-specific especially in the early stages.[42]

Facial nerve paralysis in ROCM in the literature varied between 11% to 22%.[53] In earlier reports, it was thought to be due to intracranial involvement or middle ear invasion or suppurative

parotitis.[53] Another proposed reason is facial nerve ischemia, due to edema because of the pathology of resistance arteries in diabetic patients. In most diabetics the chorda tympani is spared, the lesion is thus located distal to its bifurcation.[54] The latest belief is the spread of the infection from the pterygopalatine fossa via inferior orbital fissure, orbital apex to the infratemporal fossa.

In our study facial nerve was involved in 32% (House Brackmann Grade 2 to 4 LMN facial palsy). In half the patients it recovered completely. In another half, there was only partial or no recovery.

Osteomyelitis of the maxilla is an uncommon presentation of the RM mucormycosis. Niranjan et al in his study observed osteomyelitis of the maxilla due to fungal infection in 52% and non-fungal etiology in 48%. Histopathological report of the decalcified bone showed irregular bony trabeculae with empty osteolytic lacunae. Presence of fungal hyphae inside the bone is essential for the diagnosis of fungal osteomyelitis.[55]

3 patients in our study had histopathological features of osteomyelitis. They all presented with chronic duration of symptoms in the rhino-maxillary stage and had good outcomes with surgical and medical therapy.

Myiasis is yet another rare presentation of mucormycosis where the dead tissues are infested by larvae. Poor hygiene, low socioeconomic status, and presence of pre-existing suppurative conditions are risk factors. Foul-smelling nasal discharge, pain and passage of worms from the nose are the presenting features. These maggots cause extensive destruction of tissues. Death occurs due to meningitis.[56]

In our study, there were 2 cases of nasal myiasis. Both were recurrent mucormycosis. The probable reason is the remnants of necrotic debris for them to feed on and lack of sensation in the previously affected regions. Treatment was removal of the maggots and surgical debridement of the necrotic tissue. This sufficient in both the cases.

PATHWAY OF SPREAD

Mucor mainly spreads by angioinvasion causing mechanical and toxic damage to the intima of the blood vessel, leading to thrombosis. It later invades the lymphatics and veins also. The thrombus cause emboli and vascular obstruction responsible for tissue necrosis.[52] The penetration of endothelial cells and damage to the blood vessel lining is likely a critical step in the organism's pathogenicity. Their spores have the ability to adhere to sub-endothelial matrix proteins like type IV collagen and laminin.[48] These also have a keto-reductase system, activated in acidic pH facilitating the invasion of blood vessel walls.[13]

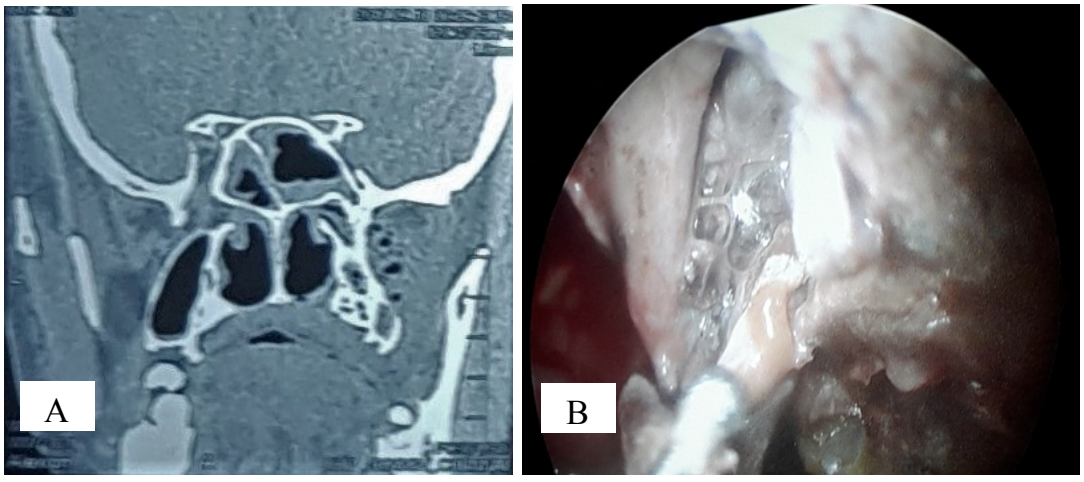
The disease usually starts in the nasal mucosa, turbinate, or palate and spreads to the paranasal sinuses. Pillsbury and Fischer proposed that infection begins in the nose and spreads to the paranasal sinuses and orbit. From there it can reach intracranially. At the optic foramen, these can cause edema, inflammation, necrosis, and damage to the ophthalmic artery and optic nerves.

Kulkarni et al. proposed the cribriform plate and the roof of the orbit which are very thin could be the portal of entry to the intracerebral area. The disease may also progress through the retro-orbital region or cause sphenoid sinus involvement. Yohai et al told that the infection may spread to the orbit via the maxillary or ethmoidal sinus or nasolacrimal duct. It may also spread via an intra-arterial route. Intracranial spread may occuur via the orbital apex or the orbital vessels or cribriform plate.

In contrary to the previous studies, Hosseini et al[17] suggested that the pterygopalatine fossa was the main of reservoir of infection. From this area, perineural spread may occur via the inferior orbital nerve or maxillary nerve. The greater palatine canal can serve as a means to spread to the hard palate. The debridement of this region, as suggested by him, may effectively seal off the gap for the spread of the disease. This had a positive impact in the survival of patients with advanced ROCM.

These were observed in our study as well. Pain and parasthesia as the initial symptoms in 80% shows the involvement of maxillary and inferior orbital nerves. The finding in 78% of our patients of attenuation of retro-maxillary area with fat plane stranding in the absence of erosion of posterior wall of maxilla in early CT scans, may serve as an evidence of pterygopalatine fossa as a potential reservoir. Except in 2 patients, all patients had an intact lamina papyraceae, which also shows a high probability of spread via the pterygopalatine fossa. From this area, via inferior orbital fissure, it can extend to the orbital apex and cavernous sinus as well.

During endoscopic debridement, the presence of greyish avascular necrotic tissue behind an intact posterior maxillary wall and thrombosis of internal maxillary artery and an intact lamina papyraceae are evidence to this theory of pathway of spread.



A - Bilateral Sphenoidal mucosal thickening with left infratemporal fossa soft tissue opacity with air pockets
B - Dirty white necrotic debris present in the left pterygopalatine fossa region

Optic nerve involvement may be due to fungi invading the orbit/ orbital apex, but the most common mechanism is probably the angioinvasion of the ophthalmic vessels leading to vision loss. Hence, the orbital or optic nerve decompression may not help in the recovery of the vision.

HISTOPATHOLOGY

There are several diagnostic techniques for mucormycosis including direct microscopy, culture, and serology with ELISA or Molecular techniques. In spite of these it is a diagnostic challenge as there are no reliable serologic, PCR-based, or skin tests at present[48]. The diagnostic confirmation is the histopathological demonstration of angioinvasion by fungi with irregular broad pauciseptate hyphae that branch at right angles,[59] often surrounded by extensive necrotic debris.[48]

As mucor is ubiquitous, it may colonize in normal people or contaminate the sample. It may also get killed while processing. Hence culture is rarely sufficient to establish the diagnosis, and a sterile culture does not rule out mucormycosis. It also delays the institution of appropriate therapy.

Galactomannan and 1,3-beta-D glucan detection tests help to rule out invasive aspergillosis.[60]

In Jeong et al's study[7], 97% diagnosed via HPE, 79% grew in cultureand species identification done in 53%. 89% diagnosd using molecular techniques. In Zaman et al's study[61] when comparing with direct microscopy, culture was positive in 48%,HPE in 94.6% and molecular techniqus in 100% with 54% species identification. Mean turnaround time was 2 hours for direct microscopy, 96±150hours for culture 72-96hours for HPE and <48hrs for molecular methods.

In our study, KOH mount or HPE was done. Due to the requirement of prompt surgical intervention, fungal culture was not a diagnostic requirement in our study. Molecular methods were not available in our hospital at the time of the study. Hence identification o the species was not done in our study. KOH smear was positive in 76% and HPE in 92%.

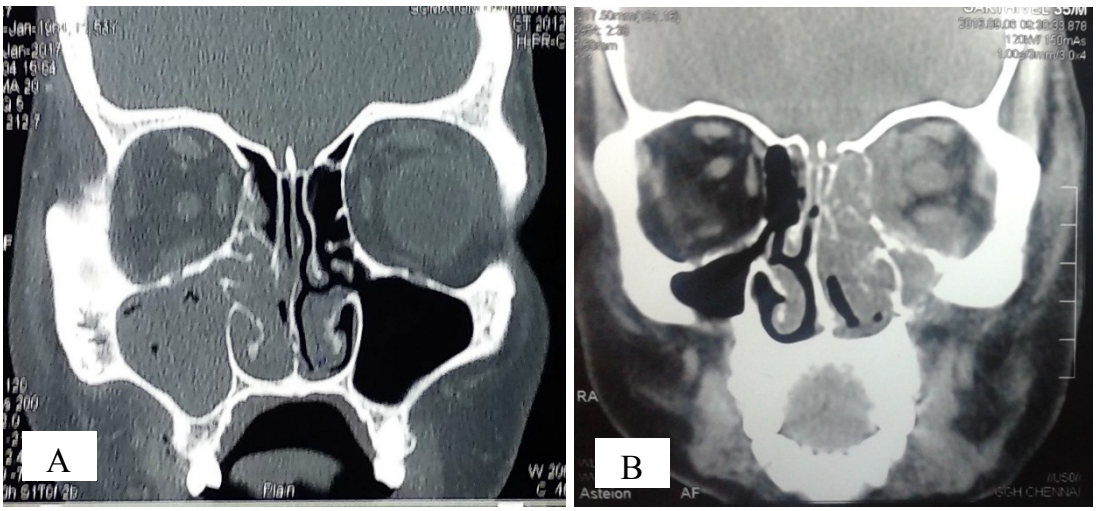
RADIOLOGY

Radiological findings are very non-specific in the early stages. Only mucosal thickening in one or more of the sinuses may be present mimicking benign mucosal disease. The main purpose of CT is the accurate delineation of the extent of the disease. Since the fungi can cross bony partitions through penetrating vessels bone erosion is not an early feature. They are particularly prone to spread across the posterolateral maxillary wall into the pterygopalatine fossa, infratemporal fossa, and pterygomaxillary fissure.[19,20]

The most frequently affected sinuses are maxillary sinus(66.7%); ethmoid sinus(53.3%) and sphenoid sinus (20%). Orbital involvement was present in six (40%) cases.[19]

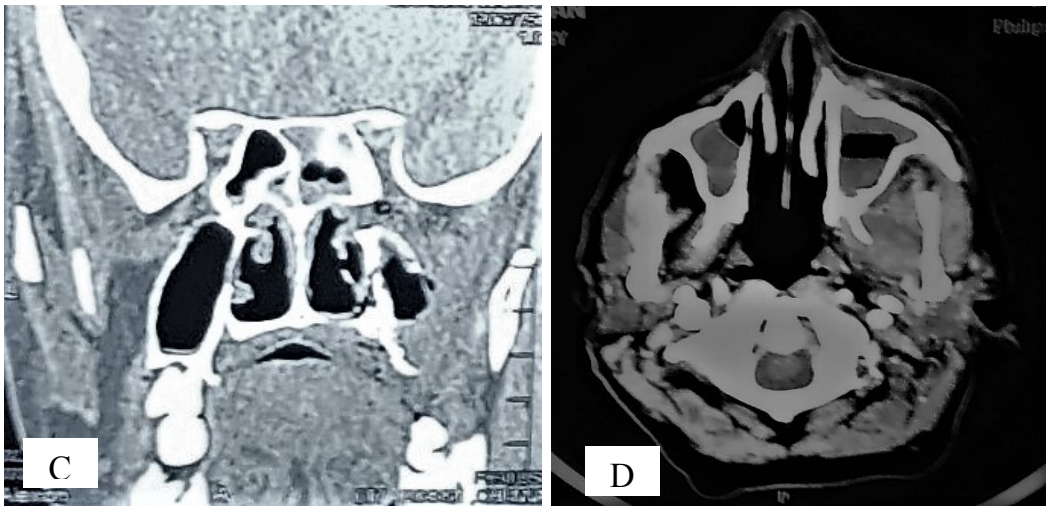
In the study by Son et al., there was a higher tendency for thickening of sinus mucosa and intraorbital extra-ocular muscle involvement in ROCM patients compared to patients with bacterial orbital cellulitis.[32]

In our study, mucosal thickening, a non-specific finding, was present in all the patients. Unilateral attenuation of the retro-maxillary area with fat plane stranding was present in 78%. Even though this is not exclusive to mucormycosis, it is an early feature that may point towards the diagnosis. This feature also stresses the retro-maxillary area as the reservoir for the disease.



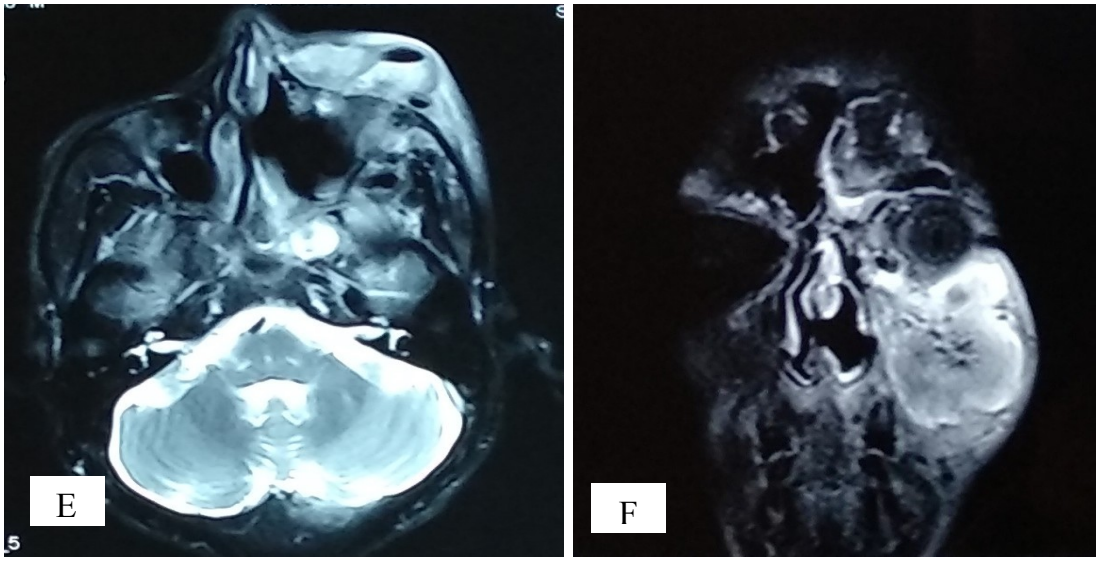
A - Soft tissue opacity in the right maxillary sinus with air pocke;. Mucosal thickening of anterior ethmoids; Involvement of cheek+

B - soft tissue opacity in the left nasal cavity, left maxillary sinus and ethmoidal sinus with left orbital extension - thickened and oedematous extraocular muscles and oedematous optic nerve



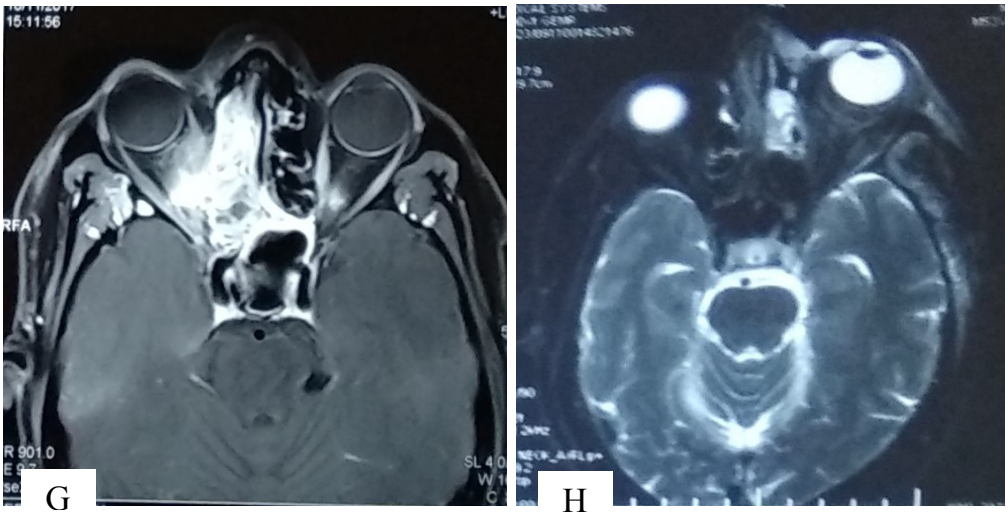
C - Involvement of the left pterygopalatine fossa and left infratemporal fossa; Mucosal thickening in the left sphenoidal sinus.

D - B/l maxillary sinusitis; Attenuation of the retro-maxillary fat plane with soft tissue stranding; Heterogeneous enhancement of the infratemporal fossa;



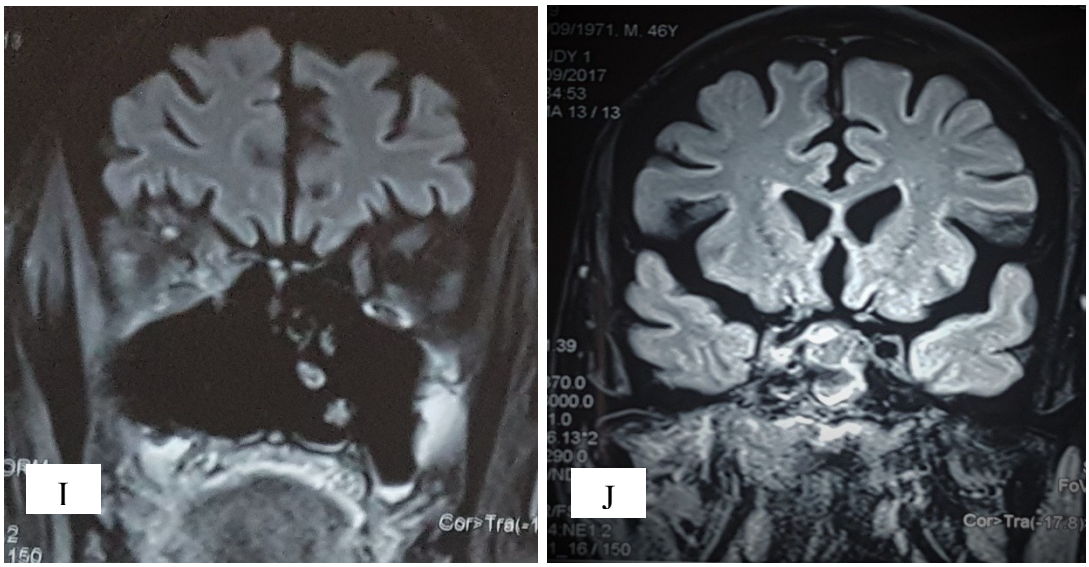
E - Left maxillary mucosal thickening; Left infratemporal fossa Soft tissue enhancement with fat plane attenuation;

F - Heterogeneous enhancement in Left premaxillary region; left preseptal cellulitis; left frontal sinus mucosal thickening



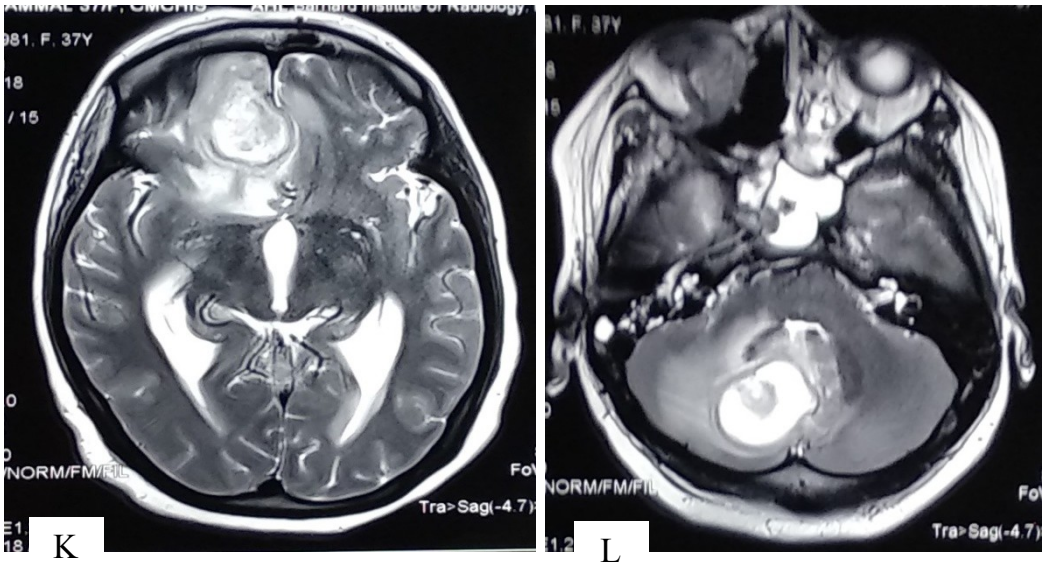
G - Hyperintense lesion in the right ethmoidal sinus; right orbital involvement

H - Left ethmoidal sinusitis; Left orbital proptosis, left preseptal cellulitis;



I - Right superior ophthalmic vein - loss of flow void

J - Right infratemporal fossa involvement with Right cavernous sinus thrombosis



K - Hyperintense frontal paramedian complex cystic lesion with perilesional edema and midline shift;

L - Sphenoidal sinusitis with a Complex cystic lesion in the right cerebellar hemisphere and vermis with perilesional edema causing an infratentorial midline shift

Bone erosion is a very late feature, before which the disease would have spread extensively. Bone erosion correlated statistically with the duration of illness. Radiological features of orbital and intracranial spread correlated statistically with the stage and outcome of the disease. Orbital involvement includes preseptal cellulitis, thickening of orbital muscles, orbital cellulitis, intraconal or extraconal lesions, or soft tissue thickening of the orbital tissue or an intraorbital mass with or without proptosis. Intracranial involvement may be cavernous sinus thrombosis or infarct or abscess intracranially.

Orbital apex involvement itself is considered as a grave sign as it can easily involve the cavernous sinus spreading fast to the opposite side and into the brain. In our study, orbital apex was involved in 19(38%) patients, cavernous sinus thrombosis in 14(28%) and involvement of the brain in 7(14%). Of these, 15/19 (79%) patients with orbital apex involvement survived even without orbital exenteration. 10/14(71%) patients with cavernous sinus thrombosis survived and 3/7(43%) with brain involvement survived. MRI was taken in a few patients for soft tissue involvements of the orbit and intracranial regions.

The black turbinate sign was described by Safder et al. in MRI. It occurs de to the occlusion of small vessels causing a lack of contrast enhancement of invaded mucosa. When present in the maxillary and ethmoidal sinusesit indicates a black mucosa sign.[32]

Magnetic resonance imaging is a useful imaging modality for the diagnosis of ROCM. The lesions are hyperintense on T2-W MRI image. Cavernous sinus thrombosis and internal carotid artery narrowing can also be seen wellin MRI. DWI adds specificity by showing restricted diffusion in the path of fungal invasion.[62]

ANTIFUNGAL THERAPY

Antifungal therapy exclusively, to control the infection is often inadequate. The hallmark angioinvasion, thrombosis, and tissue

necrosis of mucormycosis results in poor penetration of the drugs to the site of infection. Hence, in vitro susceptibility does not equate to effect in vivo.[48]

Amphotericin B is a polyene amphoteric macrolide with an internal cyclic ester and 4–7 conjugated double bonds. Due to its hydrophobic polyene domain, it is poorly soluble in aqueous media. There are four formulations are available commercially - Conventional Amphotericin-B, Amphotericin-B Colloidal Dispersion, Liposomal Amphotericin-B, Amphotericin-B Lipid complex.

The plasma concentration achieved by these formulations in increasing order is Amphotericin-B Lipid Complex<Conventional Amphotericin-B< Amphotericin-B Colloidal Dispersion<Liposomal Amphotericin-B.[22]

Jung, in his study, suggested that in indolent cases of mucormycosis in immunocompetent hosts, endoscopic sinus surgery without long-term antifungals may be sufficient, where there is no suspicious pre-operative clinical or radiological features.[15]

Deferoxamine administration, acting as an iron siderophore, appears to have a risk of developing mucormycosis, by supplying previously unavailable iron to the fungi thus enhancing its virulence. In contrast, Deferiprone and Deferasirox were fungicidal in-vitro as they

do not supply iron to this fungus. Thus as adjuvant alternative treatment option they have been used in literature.[59]

In our study, Amphotericin B was the prime drug used. 47 patients received it. Course completion was considered as 2g or above. Very few minor allergic reactions occurred and the same was manageable quite easily. The more serious problems of administering Amphotericin B were electrolyte wasting, hypokalemia, and worsening of renal parameters. Except for one patient, all others with deranged renal parameters managed to complete their course, albeit interrupted therapy. That patient was administered Liposomal Amphotericin and managed to complete the treatment. 5 patients died before completing the course of antifungal agents. 2 immunocompetent patients with unsuspecting clinical features, with histopathological diagnosis of mucormycosis post-surgery, were not started on any antifungals. On follow up one patient was normal after 6 months and another patient died after 3 months due to an accident.

Liposomal Amphotericin, a very good alternative, was not given in all patients due to its cost factor. Posaconazole, in spite of being an orally administered drug with lesser side effects, was not used as the standard drug, again, due to the cost.

SURGICAL

Surgical removal of all the necrotic tissue is the most important factor in the treatment of ROCM. But no clear guidelines are present with regards to it.

As the pterygopalatine fissure is the main reservoir for Mucor, the posterior wall of the maxillary sinus, even if intact, must always be removed irrespective of the approach or the extension of the surgery.[24]

Necrosis is not always present in the orbital tissue in ROM. It may be due to spillover inflammation from the adjacent paranasal sinuses or Mucor cellulitis. Hence, “a direct inspection of orbital contents, looking carefully for signs of necrosis", is critical in determining the need for orbital exenteration.[65]

In spite of the mixed outcomes and no clear indications, Hernandez suggested exenteration when orbital apex syndrome was associated with thrombosis of the cavernous sinus, as this implies a greater risk of intracranial extension.[24]

Repeated debridement with surveillance is mandatory for a good clearance. Frozen section can be used to guide the extent of surgery examining histologically or by staining with calcofluor.[42]

In our study, except for 3 patients all the patients underwent surgical debridement. In those 3 patients, mortality was 100%. 8 patients

underwent single surgery. Of these, 2 died in the first week, 2 of them were immunocompetent patients with indolent but histologically proven mucormycosis and 3 of them had no residual debris after the first surgery and 1 patient got discharged against medical advice. Multiple surgeries were done in 39 patients. This reduces the necrotic fungal debris load making it easier for the antifungal agents to reach and act. Also, definitive surgeries like maxillectomy or orbital exenteration may require general anaesthesia. Due to the several co-morbidities and underlying conditions, fitness for general anaesthesia is rarely obtained at the time of presentation. In the meantime, to reduce the load of fungi, endoscopic debridement under local anaesthesia is done. The advantage with mucormycosis is that due to the vascular and neural invasion, the patient does not have pain or bleeding. 42 patients underwent at least 1 procedure under local anaesthesia. Only 15 patients needed general anaesthesia for one of their procedure. 32 patients did not need any general anaesthesia in spite of the multiple surgical procedures.

During debridement, there may be purulent material, whitish or bluish unhealthy mucosa, necrotic tissue which is dirty/greyish white in colour fibrotic in consistency or blackish eschar. Usually, the normal pinkish healthy mucosa of the nasal cavity or yellowish fatty tissue of the pterygopalatine region could be clearly distinguished from the devitalized tissue. Debridement was done up to the point where pain and

fresh bleeding start to occur. Nasal douching was done to remove the crusts.

With regards to orbital or optic nerve decompression, pus was present along with occasional devitalized tissue in the orbit. The optic nerve is usually atrophied and fibrotic and does not swell upon incision of the optic nerve sheath. Hence, even with optic nerve decompression, the vision does not improve. Superior or inferior orbital fissure was also reached through the orbit with an endoscope.

During maxillectomy or sequestrectomy, the necrotic bone was easily removed as it was already devitalized and thinned. Initially, an impression compound was kept with a temporary obturator. 2 weeks later an interim obturator was given. After complete healing of the cavity, a permanent obturator was given.

A - Maxillectomy specimen

B - Post maxillectomy obturator in situ

MORTALITY

Prior to 1960, (i.e. prior to Amphotericin B), mucormycosis was almost uniformly fatal.[50] It decreased to mortality by 50%. Mortality has further decreased with awareness of early diagnosis and prompt aggressive intervention

In the meta-analysis of Roden et al, the overall mortality was 54% (504/929) with 84% in the 1950s to 47% in the 1990s. However, after 1960s Amphotericin B was widely introduced it has remained essentially unchanged.

Chakrabarti et al. also observed that ROM (91%) could be most reliably diagnosed antemortem.[32]

Hong suggests that ROCM had a better outcome compared to gastrointestinal and disseminated mucormycosis as it is diagnosed earlier and treated more easily.[63]

In the study by Jeong et al[7], overall mortality was 46%, of which the highest was in disseminated mucormycosis (68%) and least in cutaneous mucormycosis(31%). Mortality in ROCM (43%) ranged from 34% to 75% with sino-cerebral having the worst mortality (75%).

In Chakrabarti et al[9], mortality in 36 patients of ROCM in various stages were - Stage 1 – 17% stage 2 48% Stage 3 – 89%. The predictors for survival in Bhansali et al's[11] study included the lag time

between the first symptom referable to mucormycosis and treatment with Amphotericin B. Yohai et al[50] reported that patients with a lag time from seven to 12 days had a survival of 63% and those with a lag time of 13 to 30 days, it was 44%. Saedi et al's study[57], the 13.5 ±7.6 days was the mean delay between clinical presentation and diagnosis, and 16.6±7.7 days was the mean delay between clinical presentation and commencement of treatment. None of these correlated with survival. Whereas, in Ochi et al's study, in spite of initiation of treatment within 24 hrs only 4/5 survived.

In our study, the mean duration to treatment initiation was 3.92 days, with treatment initiated in 29 patients within the first 3 days. But even in such cases where treatment was started within 48 hours, there were 3 deaths which show the aggressiveness of this disease.

Rather than the correlation with a delay of treatment, it probably indicates that the severe acute fulminant presentation is probably recognized early and that less aggressive chronic forms may be more responsive to treatment.

Chakrabarti et al, Yohai et al (77% vs. 34%) and Blitzer (60% vs. 20%) et al observed that in ROCM, diabetics have a more favorable outcome than non-diabetics.

Since reversal of immunocompromised status is an important factor and DM can easily reversed compared to hematological malignancies, patients with diabetes may have a more favorable outcome.[63]

Castillo et al in his study found that HPE with multinucleate giant cell granuloma may be correlated with better prognosis and the survival decreases as the degree of angioinvasion increases.[59]

In Roden's study, of the 596/929 (64%) in whom antifungal therapy was given, survival was 62% (369/596). Of these, there was 61% survival in the 532 patients(89%) who received Amphotericin B deoxycholate. Only 3 % of those who did not receive any treatment (241 patients) survived.[6]

Combination of Amphotericin B therapy with surgery had a significantly better survival than Amphotericin B alone in several studies including Chakrabarti et al(79.6% vs. 51.7% survival),[45] Spellberg et al (86% vs. 30%)[48], Bala et al(61.5% vs. 10.3%)[26], Bhansali et al[11], Roden et al (70% vs. 57%).[6]

Also, the outcome was better in patients in whom complete surgery was done (44% vs. 14%, P = 0.04), compared to the group with incomplete surgical removal (28% vs. 57%, P = 0.046).[63]

According to Yohai et al's review[50], decreased survival rates were encountered in a delay in initiation of treatment of more than 6 days, mental status change, hemiparesis or hemiplegia, bilateral infection, non-malignant hematologic disease, renal disease, leukemia, deferoxamine therapy, and possibly facial necrosis. Blitzer et al[23] found indicators of poor prognosis as nasal deformity, hemiplegia, and facial necrosis. In the study by Talmi et al[12], increased risk factors were delayed initiation of treatment, skin necrosis, palatal involvement, bilateral disease, symptomatic intracranial involvement, exclusive medical therapy. Peterson et al[64] found diabetic ketoacidosis, significant underlying medical disorders, immunosuppressive therapy, orbital involvement, and medical management only to be associated with increased risk. Bhansali et al[11], the predictors for survival included the lag time between the first symptom and treatment with Amphotericin B, facial and lid gangrene, palatal necrosis, loss of vision, ophthalmoplegia, altered sensorium, hemiplegia, and the cerebral invasion. Chakrabarti et al[45] observed indicators of poor prognosis included a delay in treatment (> 6 days), palatal involvement, facial necrosis, orbital involvement, bilateral sinus involvement, symptomatic intracranial involvement, underlying leukemia, or deferoxamine therapy. In Jayalakshmi et al[58] study the predictors for mortality were: elderly age, intracranial extension with focal neurological deficit, immunocompromised state, for infection with zygomycosis and anemia.

The highest odds ratio was for intracranial extension with focal neurological deficit suggesting that it is the major predictor of mortality.

In our study, the overall mortality was 10%. The reason for this might be because of the early diagnosis, prompt treatment, and reversal of the underlying factors. The early diagnosis may be due to the fact that rhino-orbito-cerebral mucormycosis presents with early signs and symptoms and examination of the same is easily feasible. The second reason being, in our study 88% of the patients had diabetes mellitus as their underlying condition which is easily reversible. Thus metabolic stability can be attained with more ease compared to other conditions like hematological malignancies or immunosuppression due to transplantation. The final, rather important reason might be due to heightened awareness about mucormycosis in our setup.

In our study, there was no significant correlation between age or sex of the patient and the outcome of the disease. Among the risk factors, diabetic ketoacidosis and electrolyte imbalance are the main significantly correlating factors. Altered GCS was the only symptom that statistically predicted a worse outcome. In the radiological investigations, orbital apex syndrome, cavernous sinus thrombosis and involvement of the brain – all three correlated statistically with a worse outcome. As expected the stage of presentation also correlated statistically with the outcome of the disease.

The factor that was not considered in our study is the outcome correlation with the species causing the disease. This, along with the immunocompromised state, might be the reason why in spite of initiation of treatment within 48 hrs 3 patients died and some patients were stable even after 45 days.

FOLLOW - UP

In our study, weekly endoscopic examination and if needed debridement were done. Once the patients had a completely mucosalised cavity, they were discharged. Initial review was after 2 weeks. Later, the patients were reviewed every month for 6 months. As and when needed CT scan was taken. The cranial nerve functions recovered partially or did not recover. Vision loss was permanent. But cheek swelling and orbital cellulitis resolved in all cases.

RECENT ADVANCES

Recent studies have shown that the uptake of Mucorales into the airway epithelial cells is governed by EGFR signaling which subsequent causes damage. Treatment with gefitinib, EGFR inhibitor, in animal studies, reduced tissue fungal load of target organs and significantly increased survival. Since the target is the host EGFR receptors, acquisition of drug resistance in the fungus is less likely to occur.[66]

CONCLUSION

- In our study, the most common underlying factor was diabetes mellitus. But, rather than the mere presence of diabetes mellitus, it was the control of diabetes and diabetic ketoacidotic state that correlated with the stage of the disease and outcome. Electrolyte imbalance also played a massive role in the outcome of the mucormycosis.

- Lack of anaesthesia and lack of bleeding are two extremely vital signs for the diagnosis of mucormycosis.

- In spite of radiological changes being subtle and inconclusive in the early stages, evidence of retro-maxillary fat plane stranding and attenuation of the soft tissue in the CT scan and hyperintense lesion in the retro-maxillary area in an MRI scan, serve as early radiological pointers towards mucormycosis. Bone erosion occurs in late stages of the disease.

- Pterygopalatine fossa involvement, suspected as the reservoir of infection, was present in our study as well. Conclusive evidence were present with regards to both radiology, as mentioned above, and surgery. During surgery, there was presence of devitalized tissue in the region of the pterygopalatine area, in spite of an intact posterior maxillary wall.

- As there is lack of sensation of the dead necrotic tissue, the patients can be taken up for immediate surgical debridement at the time of presentation itself with minimal local anaesthesia or no anaesthesia. This by-passes the need for general anaesthesia, for which the patient might not be fit due to the underlying risk factors. This was probably the cause for the high survival rate in our study.

- Multiple surgical procedures, under local and/or general anaesthesia, alongside completion of the antifungal course massively influences the outcome.

BIBLIOGRAPHY

1) Luna B, Drew RH, Perfect JR. Agents for treatment of invasive fungal infections. Otolaryngol Clin North Am [Internet]. 2000;33(2):277–99. Available from: http://dx.doi.org/ 10.1016/ S0030 -6665(00)80005-5

2) Thrasher RD, Kingdom TT. Fungal infections of the head and neck: An update. Otolaryngol Clin North Am. 2003;36(4):577–94.

3) Mitchell TG. Overview of basic medical mycology. Otolaryngol Clin North Am [Internet]. 2000;33(2):237–49. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80003-1

4) Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am [Internet]. 2000;33(2):349–65. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80010-9

5) Gillespie MB, O'malley BW. An algorithmic approach to the diagnosis and management of invasive fungal rhinosinusitis in the immunocompromised patient. Otolaryngol Clin North Am [Internet]. 2000;33(2):323–34. Available from: http://dx.doi. org/10. 1016/S0030-6665(00)80008-0

6) Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and Outcome of

Zygomycosis: A Review of 929 Reported Cases. Clin Infect Dis [Internet]. 2005;41(5):634–53. Available from: https://academic. oup.com/ cid/article-lookup/doi/10.1086/432579

7) Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2018;

8) Corzo-León DE, Chora-Hernández LD, Rodríguez-Zulueta AP, Walsh TJ. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: Epidemiology, diagnosis, and outcomes of reported cases. Med Mycol. 2018;56(1):29–43.

9) Chakrabarti A, Chatterjee SS, Das A, Panda N, Shivaprakash MR, Kaur A, et al. Invasive zygomycosis in India: Experience in a tertiary care hospital. Postgrad Med J. 2009;85(1009):573–81.

10) Kolekar JS. Rhinocerebral Mucormycosis: A Retrospective Study. Indian J Otolaryngol Head Neck Surg. 2014;67(1):93–6.

11) Bhansali A, Bhadada S, Sharma A, Suresh V, Gupta A, Singh P, et al. Presentation and outcome of rhino-orbital-cerebral mucormycosis in patients with diabetes. Postgrad Med J. 2004;80(949):670–4.

12) Talmi YP, Goldschmied-Reouven A, Bakon M, Barshack I, Wolf M, Horowitz Z, et al. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol - Head Neck Surg. 2002;127(1):22–31.

13) Abdollahi A, Shokohi T, Amirrajab N, Poormosa R, Am K, Sj M, et al. Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis- A retrospective analysis. 2016;2(4):15–23.

14) Mignogna MD, Fortuna G, Leuci S, Adamo D, Ruoppo E, Siano M, et al. Mucormycosis in immunocompetent patients: A case-series of patients with maxillary sinus involvement and a critical review of the literature. Int J Infect Dis [Internet]. 2011;15(8):e533–40. Available from: http://dx.doi.org/ 10.10 16/j.ijid.20 11.02.005

15) Jung H, Park SK. Indolent mucormycosis of the paranasal sinus in immunocompetent patients: Are antifungal drugs needed? J Laryngol Otol. 2013;127(9):872–5.

16) Sundaram C, Sravani T, Uppin S, Uppin M. Rhinocerebral mucormycosis: Pathology revisited with emphasis on perineural spread. Neurol India [Internet]. 2014;62(4):383. Available from: http://www.neurologyindia.com/text.asp?2014/62/4/383/141252

17) Hosseini SMS, Borghei P. Rhinocerebral mucormycosis: Pathways of spread. Eur Arch Oto-Rhino-Laryngology. 2005;262(11):932–8.

18) Prado-Calleros HM, Fajardo-Dolci G, Plowes-Hernández O, Jiménez-Gutiérrez C. Rhino-Orbital Mucormycosis. Cohort study of its treatment according disease extent and reversion of its pathophysiology . Gac Med Mex [Internet]. 2016;152(6):770–82. Available from: https://www.scopus. com/ inward/ record. uri?eid=2-s2.0-85006039243& partnerID= 40& md5= a331f64fc ca72442b4437 1473e 7af070

19) Raab P, Sedlacek L, Buchholz S, Stolle S, Lanfermann H. Imaging Patterns of Rhino-Orbital-Cerebral Mucormycosis in Immunocompromised Patients: When to Suspect Complicated Mucormycosis. Clin Neuroradiol. 2017;27(4):469–75.

20) Gamba JL, Woodruff WW, Djang WT, Yeates AE. Craniofacial mucormycosis: assessment with CT. Http://DxDoi Org/ 101148/ Radiology16013715034. 1986;

21) Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, et al. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect [Internet]. 2014;20(5):O336–9. Available from: http://dx.doi.org/10.1111/1469-0691.12408

22) Shah K, Dave V, Bradoo R, Shinde C, Prathibha M. Orbital Exenteration in Rhino-Orbito-Cerebral Mucormycosis: A

Prospective Analytical Study with Scoring System. Indian J Otolaryngol Head Neck Surg [Internet]. 2018; Available from: http://link.springer.com/10.1007/s12070-018-1293-8

23) RM Pt survival factors Blitzer 179.pdf.

24) Plowes Hernandez O, Prado Calleros HM, Soberon Marmissolle Daguerre GS, Sadek Gonzalez A. Rhino-orbito-cerebral mucormycosis. Management strategies to avoid or limit intracraneal affection and improve survival. Acta Otorrinolaringol Esp. 2015;66(6):348–52.

25) Chander J, Kaur M, Singla N, Punia R, Singhal S, Attri A, et al. Mucormycosis: Battle with the Deadly Enemy over a Five-Year Period in India. J Fungi [Internet]. 2018;4(2):46. Available from: http://www.mdpi.com/2309-608X/4/2/46

26) Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in north India: Experience from a tertiary care hospital. Med Mycol. 2015;53(3):248–57.

27) Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis—The bitter and the sweet. PLoS Pathog. 2017;13(8):1–9.

28) Katragkou A, Walsh TJ, Roilides E. Why is mucormycosis more difficult to cure than more common mycoses? Clin Microbiol

Infect [Internet]. 2014;20(6):74–81. Available from: http://dx.doi.org/10.1111/1469-0691.12466

29) Frater JL, Hall GS, Procop GW. Histologic features of zygomycosis: Emphasis on perineural invasion and fungal morphology. Arch Pathol Lab Med. 2001;125(3):375–8.

30) Ferguson BJ. Definitions of fungal rhinosinusitis. Otolaryngol Clin North Am [Internet]. 2000;33(2):227–35. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80002-X

31) Schell WA. Histopathology of fungal rhinosinusitis. Otolaryngol Clin North Am [Internet]. 2000;33(2):251–76. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80004-3

32) Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: A review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect [Internet]. 2004;10(SUPPL. 1):31–47. Available from: http://dx.doi.org /10 .1111 /j. 1470-9465. 2004.00843.x

33) Epstein VA, Kern RC. Invasive Fungal Sinusitis and Complications of Rhinosinusitis. Otolaryngol Clin North Am. 2008;41(3):497–524.

34) Chakrabarti A. Mucormycosis in Asia : Where do we stand now

35) Sikora AG, Lee KC. Otolaryngologic manifestations of immunodeficiency. Otolaryngol Clin North Am. 2003;36(4):647–72.

36) Mirza N, Lanza DC. Diagnosis and management of rhinosinusitis before scheduled immunosuppression: A schematic approach to the prevention of acute fungal rhinosinusitis. Otolaryngol Clin North Am [Internet]. 2000;33(2):313–21. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80007-9

37) Malani PN, Kauffman CA. Prevention and prophylaxis of invasive fungal sinusitis in the immunocompromised patient. Otolaryngol Clin North Am [Internet]. 2000;33(2):301–12. Available from: http://dx.doi.org/10.1016/S0030-6665(00)80006-7

38) Luk LJ, DelGaudio JM. Topical Drug Therapies for Chronic Rhinosinusitis. Otolaryngol Clin North Am. 2017;50(3):533–43.

39) McDonald PJ. Mucormycosis (Zygomycosis): Background, Etiology and Pathophysiology, Epidemiology [Internet]. Medscape. 2017. Available from: https://emedicine. medscape. com/ articl e/22255 1-overvi ew?pa= TSLoMNsCiqGTHo 3qSKjNzuA SuZiT% 2F88K Dd6bpyqa4HU BJvJ6LEvac NTXzyS% 2FQV JM56MI7d GTgNawP fsOtJla9Q%3 D%3D#sho wall

40) Lewis RE, Lortholary O, Spellberg B, Roilides E, Kontoyiannis DP, Walsh TJ. How does antifungal pharmacology differ for mucormycosis versus aspergillosis? Clin Infect Dis. 2012;54(SUPPL. 1):67–73.

41) Binder U, Maurer E, Lass-Flörl C. Mucormycosis - from the pathogens to the disease. Clin Microbiol Infect. 2014;20(6):60–6.

42) Gamaletsou MN, Sipsas N V., Roilides E, Walsh TJ. Rhino-Orbital-Cerebral mucormycosis. Curr Infect Dis Rep. 2012;14(4):423–34.

43) Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54(SUPPL. 1):23–34.

44) Chakrabarti A, Singh R. Mucormycosis in India: Unique features. Mycoses. 2014;57(s3):85–90.

45) Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol. 2006;44(4):335–42.

46) Mallis A, Mastronikolis SN, Naxakis SS, Papadas AT. Rhinocerebral mucormycosis: An update. Eur Rev Med Pharmacol Sci. 2010;14(11):987–92.

47) Babu SV, Venkatesh U, Prasannaraj T, Shivaprakash K V., Prathima S. Sinonasal mucormycosis: A series of seven cases. Clin Rhinol. 2012;5(1):25–7.

48) Spellberg B, Edwards J, Ibrahim A. Novel perspectives on Mucormycosis: pathopsyology, presentation, and management. Clin Microbiol Rev. 2005;18(3):556–69.

49) Patel AK, Patel KK, Patel K, Gohel S, Chakrabarti A. Mucormycosis at a tertiary care centre in Gujarat, India. Mycoses. 2017;60(6):407–11.

50) Factors S, Mucormycosis R. MAJOR REVIEW Survival Factors in Rhino-Orbital-Cerebral. 1994;39(1).

51) Sachdeva K. Rhino-oculo Cerebral Mucormycosis with Multiple Cranial Nerve Palsy in Diabetic Patient: Review of Six Cases. Indian J Otolaryngol Head Neck Surg. 2013;65(4):375–9.

52) Jiang N, Zhao G, Yang S, Lin J, Hu L, Che C, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol [Internet]. 2016;16(1):1–7. Available from: http://dx.doi.org/10.1186/s12886-016-0189-1

53) MS S, Menezes V, VV S, AM B. Institutional experience of mucormycosis over a period of 10 years - retrospective case

series. Int J Adv Med [Internet]. 2014;1(2):1. Available from: http://www.ijmedicine.com/?mno=165762

54) Shekar V, Sikander J, Rangdhol V, Naidu M. Facial nerve paralysis: A case report of rare complication in uncontrolled diabetic patient with mucormycosis. J Nat Sci Biol Med [Internet]. 2015;6(1):226–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4367044&tool=pmcentrez&rendertype=abstract

55) Urs AB, Singh H, Mohanty S, Sharma P. Fungal osteomyelitis of maxillofacial bones: Rare presentation. J Oral Maxillofac Pathol [Internet]. 2016;20(3):546. Available from: http://www.ncbi. nlm.nih. gov/pubmed/2 7721629%5Cnhttp: /www.pub medcentral. nih.gov/articlerender.fcgi?art id=PMC5051312

56) Abu El-Naaj I, Leiser Y, Wolff A, Peled M. The surgical management of rhinocerebral mucormycosis. J Cranio-Maxillofacial Surg [Internet]. 2013;41(4):291–5. Available from: http://dx.doi.org/10.1016/j.jcms.2012.03.019

57) Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. J Laryngol Otol. 2011;125(8):807–10.

58) Jayalakshmi SS, Reddy RG, Borgohain R, Subramanyam C, Panigrahi M, Sundaram C, et al. Predictors of mortality in rhinocerebral mycosis Th is a PD si F te i ho s a st va (w ed ila w by ble w. mMfo ed ed r fr kn kn ee ow ow do . c Pu w om b nl o). lica ad tio fr ns om Th is a PD si F te i ho s a st va (w ed ila w by ble w . m M fo ed e. 2007;55(3):6–8.

59) Aggarwal SK. Invasive Sino-orbito-cerebral mycosis-An Overview. Indian J Clin Exp Ophthalmol [Internet]. 2015;1(3):149. Available from: http://www indianjournals.com/I jor.aspx ?target=ijor:ijceo&volume=1&issue=3&article=006

60) Bulent Ertugrul M, Arikan-Akdagli S. Mucormycosis [Internet]. Emerging Infectious Diseases: Clinical Case Studies. Elsevier Inc.; 2014. 309-321 p. Available from: http://dx.doi .org/10.10 16/B978-0-1 2-416975-3.000 23-6

61) Zaman K, Rudramurthy SM, Das A, Panda N, Honnavar P, Kaur H, et al. Molecular diagnosis of rhino-orbito-cerebral mucormycosis from fresh tissue samples. J Med Microbiol. 2017;66(8):1124–9.

62) Wani N, Jehangir M, Lone P. Rhino-orbito-cerebral mucormycosis: Magnetic resonance imaging. Indian J Otol [Internet]. 2015;21(3):215. Available from: http://www .i ndianj otol.org/tex t .asp?2015/21/3/215/159700

63) Hong H-L, Lee Y-M, Kim T, Lee J-Y, Chung Y-S, Kim M-N, et al. Risk Factors for Mortality in Patients with Invasive Mucormycosis. Infect Chemother [Internet]. 2013;45(3):292. Available from: https://synapse.ko reamed .org /DOIx . php ?id=10.3947/ic.2013.45.3.292

64) Peterson KL, Wang M, Canalis RF, Abemayor E. 1997-Rhinocerebral Mucormycosis-Evolution of dis and tx option.pdf. 1997;(July).

65) Avet P, Kline L, Sillers M. Endoscopic sinus surgery in the management of mucormycosis. J Neuro-ophthalmology [Internet]. 1999;19(1):56–61. Available from: http://journals.lww.com/ jneuro-ophthalmology/ Abstract/ 1999/ 03000 /Endoscopic_ Sinus_ Surgery_ in_ the_ Management_ of.20.aspx

66) Watkins TN, Gebremariam T, Swidergall M, Shetty AC, Graf KT, Alqarihi A, et al. Inhibition of EGFR Signaling Protects from Mucormycosis. MBio [Internet]. 2018;9(4):e01384-18. Available from: http://mbio.asdm.org/content/9/4/e01384-18.abstract?cpetoc

67) Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. Curr Infect Dis Rep. 2010;12(6):423–9.

PATIENT CONSENT FORM

Title of the Project : "A Study on Rhino-Orbital Mucormycosis-Etiopathogenesis, Risk Factors and Management"

Institution : Upgraded Institute of Otorhinolaryngology,
Madras Medical College,
Chennai – 600003.

Name :
Age :
Sex :

Date :
IP No. :
Project Patient No. :

The details of the study have been provided to me in writing and explained to me in my own language.

I confirm that I have understood the above study and had the opportunity to ask questions.

I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

I have been given an information sheet giving details of the study.

I fully consent to participate in the above study.

_____	_____	_____
Name of the subject	Signature	Date
_____	_____	_____
Name of the Investigator	Signature	Date

INFORMATION SHEET

- We are conducting **"A Study on Rhino-Orbital Mucormycosis-Etiopathogenesis, Risk Factors and Management"** at the Upgraded Institute of Otorhinolaryngology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai – 600003.

- In this study the occult positivity rate of the Oropharyngeal Malignancies with N0 neck is studied by doing Selective Neck Dissection for all the patients in the inclusion criteria and examining the histopathology report of their neck nodes.

- At the time of announcing the results and suggestions, name and identity of the patients will be confidential.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator **Signature of Participant**

Date :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Raghavi
I Year Post Graduate in MS ENT
Upgraded Institute of Oto-rhinolaryngology
Madras Medical College
Chennai 600 003

Dear Dr.Raghavi,

The Institutional Ethics Committee has considered your request and approved your study titled **"A STUDY ON RHINO-ORBITAL MUCORMYCOSIS – ETIOPATHOGENESIS, RISK FACTORS AND MANAGEMENT" - NO.14072017**

The following members of Ethics Committee were present in the meeting hold on **07.07.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., Dean MMC,Ch-3	:Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
5. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6. Prof.Shanthy Gunasingh, Director, Inst. of Social Obstetrics,KGH	: Member
7. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
8. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MUCORMYCOSIS QUESTIONNAIRE

1. Name :
2. Age :
3. Sex :
4. Date/Month of presentation:
5. Address :
6. Occupation :
7. Duration of illness :
8. SYMPTOM
    a. Initial symptom :
    b. Nasal Symptoms :
        i. Onset & Progression:
        ii. Other specific symptoms :
    c. Vision :
        i. At the time of presentation:
        ii. During the treatment :
        iii. After recovery :
    d. Involvement of other cranial Nerves:
        i. At the time of presentation:
        ii. During the treatment :
        iii. After recovery :
9. Time interval between first symptom and first doctor visit :
10. Time interval between first symptom and diagnosis :
11. Time interval between first symptom and initiation of treatment:
12. Stage of presentation :
13. Comorbidities :
    a. Diabetes :
        i. Yes/No :
        ii. Duration :
        iii. Regular treatment :
        iv. Under control :
        v. HbA1c :

b. Immunocompromised Status:
    i. Yes/No :
    ii. Duration :
    iii. Regular Treatment :
    iv. Under control :

14. Investigations :
    a. Blood Investigations:
        i. Complete blood count :
        ii. Glycemic Status & HbA1c :
        iii. Renal Parameters :
        iv. Special Investigations :
    b. Diagnostic Nasal Endoscopic Findings:
    c. CT :
    d. MRI :
    e. Biopsy :
    f. Fungal KOH smear :
    g. Fungal Culture Sensitivity :
15. Medical management :
    a. Drug :
    b. Duration :
16. Surgical management :
17. Response to treatment :
    a. Stage of presentation :
    b. Time of initiation of treatment:
    c. Comparison of comorbidities:
    d. Treatment adapted :
    e. Outcome of the patient :
18. Follow up :
    a. 3 months :
    b. 6 months :

ஆராய்ச்சி ஒப்புதல் படிவம்

ரைனோ ஆர்பிட்டல் மியூக்கர் மைக்கோசிஸ்-ன் ஆபத்தான அம்சங்கள் மற்றும் தொற்று தாக்குதலில் இருந்து மீட்பது குறித்த ஆய்வு

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
எண்	:	ஆராய்ச்சி சேர்க்கை எண்	:
பால்	:		

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்குத் தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும் சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

தேதி

<u>ஆராய்ச்சி தகவல்தாள்</u>

ஆராய்ச்சியாளர் பெயர் :

ரைனோ ஆர்பிட்டல் மியூக்கர் மைக்கோசிஸ்-ன் ஆபத்தான அம்சங்கள் மற்றும் தொற்று தாக்குதலில் இருந்து மீட்பது குறித்த ஆய்வு

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் நோயாளிகளிடம் ரைனோ ஆர்பிட்டல் மியூக்கர் மைக்கோசிஸ்-ன் ஆபத்தான அம்சங்கள் மற்றும் தொற்று தாக்குதலில் இருந்து மீட்பது குறித்த ஆய்வு.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில பரிசோதனைக்கு உட்படுத்து அதன் தகவல்களை ஆராய்வோம். இதனால் உங்களுடைய சிகிச்சைக்கு பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

---------- ----------

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி

A STUDY ON RHINO-ORBITAL MUCORMYCOSIS

Patient Details						Complaints and clinical features															Risk Factors															DNE Findings					Radiology						Biopsy		Treatment								Outcome		
S. No	Name	Age	Sex	Month of presentation	Occupation	Duration of illness	Treatmetnt Initiation	fever	nasal obstruction	nasal discharge	headache	Eye edema	Loss of vision	EOM fixed	proptosis	cheek swelling	palate	facial nerve	trigeminal nerve	altered gcs	Previous antibiotics	DM	duration	Regular Rx	control	DKA	Electrolyte Imbalance	Others	HT	Smoker	Alcoholic	Nephro	anaemia	eschar	pus	unhealthy mucosa	both nasal cavity	sinusitis	bone erosion	Retromaxillary area	orbital apex	cavernous sinus	Brain infarct	Only mucor	Mixed fungal	blood transfusion	debridement	maxillectomy	orbital decompression	ampho	liposomal ampho	posaconazole	itraconazole	Stage	Antifungals	Number of Surgery	Treatment stratergy	Outcome	Followup
1	Nagurbee	40	F	July 2016	House wife	20d	1d	-	+	-	+	-	-	-	-	+	+	+	+	-	+	+	7y	-	-	+	+	steroids	-	-	-	+	-	+	+	+	-	+	-	+	+	+	-	+	-	2	-	-	400 mg	3g		-	RO CM	AF	MS	MS AF MC	G	6m G
2	Varalakshmi	58	F	July 2016	House wife	25d	2d	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	5y	-	-	+	+	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	1	-	-	400 mg	-	-	-	RO CM	IAF	SS	SS IAF DC	D	D 1w
3	Rajeshwari	35	F	August 2016	House wife	20d	4d	-	+	+	-	+	+	+	+	+	-	-	+	-	-	+	3y	+	-	-	-	SLE Steroids	-	-	-	+	+	+	+	+	-	+	-	-	-	+	-	+	2	-	1	2g	-	-	-	RO M	AF	MS	MS AF DC	G	D SLE
4	Sakthivel	35	M	September 2016	Call center	10d	10d	-	+	+	+	+	+	+	+	+	+	-	+	-	-	+	1y	+	-	-	-	-	-	-	-	+	-	-	+	+	+	-	-	-	-	-	+	-	1	-	1	-	-	-	1m	RO M	IAF	SS	SS IAF IDC	G	D 3m accident
5	Palaniappan	49	M	October 2016	Farmer	6d	8d	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	5y	-	-	-	-	Rec	-	+	+	-	+	+	-	+	+	+	+	+	-	-	+	-	+	2	1	1	2g	-	-	-	RO M	AF	MS	MS AF DC	G	2y G
6	Anjalai	45	F	November 2016	Maid	25d	5d	-	-	+	+	-	-	-	-	+	-	-	+	-	+	+	5y	+	+	-	-	Rec	-	-	-	-	-	-	+	+	+	-	-	-	-	-	+	-	-	1	-	-	2g	-	-	6m	RM	AF	SS	SS AF	G	1.5y G
7	Dilli	79	M	November 2016	Farmer	25d	3d	+	+	+	-	+	+	+	+	+	+	-	+	-	+	-	-	-	0	-	-	Rec	-	-	-	-	-	+	+	+	-	+	+	+	-	-	+	-	-	3	-	-	2g	-	-	-	RM	AF	MS	MS AF	G	1y G
8	Paramasivam	66	M	November 2016	Farmer	30d	0d	-	+	+	+	-	-	-	-	+	+	+	+	-	-	+	15y	-	-	-	+	-	-	-	+	+	-	+	-	+	-	+	+	+	-	-	+	-	-	4	1	-	2g	-	4w	-	RM	AF	MS	MS AF MC	G	6m G
9	Ayyavu	64	M	January 2017	Salesman	30d	4d	-	+	+	-	-	-	-	-	+	+	-	+	-	-	+	0.6y	+	+	-	-	-	-	+	+	-	-	+	+	+	-	+	+	+	-	-	+	-	-	5	-	-	656 mg	-	-	-	RM	IAF	MS	MS IAF DC	G	6m G
10	Chinnadurai	51	M	January 2017	Tailor	10d	0d	-	+	+	+	+	+	+	+	+	-	+	+	+	-	+	5y	-	-	+	+	-	-	+	+	+	+	+	+	-	+	+	+	-	-	+	-	+	-	-	-	200 mg	-	-	-	RO M	IAF	NS	IAF IMC	D	D
11	Chinnathambi	60	M	January 2017	Farmer	45d	3d	-	+	+	+	-	-	-	-	-	-	-	-	-	+	+	15y	+	+	-	-	-	+	+	+	-	-	+	+	+	-	+	-	+	-	-	-	+	-	3	-	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	6m G
12	Pappa	45	F	January 2017	Farmer	40d	5d	-	+	-	+	+	+	+	+	+	-	+	+	-	-	+	5y	-	-	-	+	-	-	-	-	+	+	+	+	+	-	+	-	-	-	-	+	-	-	1	-	-	500 mg	-	-	-	RO M	IAF	SS	SS IAF IDC	G	LTF
13	Anu	37	F	February 2017	Maid	7d	3d	-	+	-	+	+	+	+	+	+	-	-	-	-	+	+	2y	-	-	-	-	Rec	-	-	-	-	-	+	-	+	-	+	+	+	-	-	+	-	-	2	-	1	2g	-	-	6m	RO CM	AF	MS	MSA F DC	G	1y G
14	Bose	72	M	February 2017	Tailor	12d	2d	-	+	+	+	-	-	-	-	-	-	-	-	-	-	+	5y	+	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	-	-	-	+	-	-	3	-	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	6m G
15	Jamuna	41	F	February 2017	Maid	25d	10d	-	-	-	-	+	+	+	+	-	-	-	+	-	+	-	-	-	0	-	-	Rec	-	-	-	-	-	-	+	+	-	+	-	-	-	-	+	-	-	1	-	-	100 mg	-	-	-	RO M	IAF	SS	IAF	G	1.5y G
16	Porkodi	53	F	February 2017	House wife	15d	0d	+	+	+	+	+	-	-	-	+	+	+	+	-	-	+	10y	+	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	-	-	+	-	-	3	1	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	1.5y G
17	Tamilselvi	55	F	February 2017	House wife	10d	4d	-	+	-	+	+	+	+	+	+	-	+	+	-	+	+	20y	+	-	-	+	steroids	+	-	-	+	+	+	+	-	+	-	+	+	+	-	+	-	-	3	-	1	2g	2g	-	-	RO M	AF	MS	MS AF MC	G	6m G
18	Anitha	31	F	March 2017	House wife	30d	0d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	5y	-	-	+	+	HIV	-	-	-	+	+	+	+	+	-	+	-	+	+	+	-	+	-	+	2	1	1	2g	-	-	1m	RO CM	AF	MS	MS AF MC	G	LTF
19	Balakrishnan	60	M	March 2017	Cooli	8d	2d	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	10y	-	-	+	+	-	+	+	+	+	-	+	+	+	-	+	-	+	+	+	+	+	-	-	-	-	-	216 mg	-	-	-	RO CM	IAF	NS	IAF IMC	D	D
20	Kannan	50	M	March 2017	Labourer	5d	3d	+	+	-	+	+	+	+	+	-	-	+	-	-	+	+	New	-	-	+	+	-	-	-	-	+	-	+	+	+	-	+	-	+	-	-	+	-	-	2	-	1	2g	-		-	RO M	AF	MS	MS AF MC	G	6m G
21	Krishnan	45	M	March 2017	Labourer	30d	15d	-	+	-	+	+	+	+	+	-	-	-	+	-	+	+	7y	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	-	+	-	-	3	-	1	3g	-	-	-	RO CM	AF	MS	MS AF DC	G	6m G
22	Mythili	57	F	March 2017	House wife	2d	0d	-	+	+	-	+	+	+	+	-	-	-	+	-	+	+	10y	+	-	+	+	-	-	-	-	-	+	+	+	+	+	-	+	+	+	-	-	+	-	-	3	-	1	3g	-	-	-	RO M	AF	MS	MS AF MC	G	LTF

S. No	Name	Age	Sex	Month of presentation	Occupation	Duration of illness	Treatmetnt Initiation	fever	nasal obstruction	nasal discharge	headache	Eye edema	Loss of vision	EOM fixed	proptosis	cheek swelling	palate	facial nerve	trigeminal nerve	altered gcs	Previous antibiotics	DM	duration	Regular Rx	control	DKA	Electrolyte Imbalance	Others	HT	Smoker	Alcoholic	Nephro	anaemia	eschar	pus	unhealthy mucosa	both nasal cavity	sinusitis	bone erosion	Retromaxillary area	orbital apex	cavernous sinus	Brain infarct	Only mucor	Mixed fungal	blood transfusion	debridement	maxillectomy	orbital decompression	ampho	liposomal ampho	posaconazole	itraconazole	Stage	Antifungals	Number of Surgery	Treatment stratergy	Outcome	Followup
23	Sulochana	65	F	March 2017	House wife	6d	2d	-	+	-	+	+	+	+	+	+	-	+	+	-	+	+	20y	+	+	+	+	Hbs Ag	-	-	-	+	+	+	+	+	-	+	+	+	+	-	+	-	-	3	-	1	2g	-	-	-	RO CM	AF	MS	MS AF DC	G	1y G
24	Jayalakshmi	55	F	April 2017	House wife	8d	1d	-	+	+	+	+	-	-	+	-	-	-	-	-	+	New	-	-	+	-	-	-	-	-	-	+	+	+	-	+	+	-	-	2	-	-	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
25	Madhamma	68	F	April 2017	Farmer	20d	0d	-	+	+	+	+	-	-	+	+	-	-	+	-	-	+	12y	-	-	-	-	-	+	-	-	+	-	-	+	+	-	+	-	-	-	-	+	-	-	2	-	1	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
26	Mohanraj	42	M	April 2017	Cottonmill worker	15d	4d	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	5y	-	-	+	+	-	-	+	+	-	-	-	+	+	-	+	+	+	+	+	+	-	-	-	-	-	600 mg	-	-	-	RO CM	IAF	NS	IAF IMC	D	D
27	Ramadevi	55	F	April 2017	House wife	35d	5d	+	+	+	+	-	+	+	-	+	+	+	+	-	-	+	15y	+	-	-	+	-	-	-	-	+	-	+	-	+	+	+	+	+	-	-	-	+	-	-	3	-	-	2g	-	4w	-	RO M	AF	MS	MS AF MC	G	6m G
28	Ganesan	46	M	June 2017	Farmer	10d	0d	-	+	+	-	-	-	-	-	+	+	+	+	-	+	+	12y	+	-	-	-	-	+	-	-	+	-	+	+	+	-	+	-	+	-	-	+	-	-	3	1	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	6m G
29	Gunasekaran	60	M	June 2017	Farmer	40d	10d	-	+	-	+	+	+	-	+	+	-	-	+	-	-	-	-	+	0	-	-	-	-	-	+	-	-	+	+	-	+	-	-	-	-	+	-	-	2	-	1	2g	-	-	-	RO M	AF	MS	MS AF	G	6m G
30	Indumathy	36	F	June 2017	Maid	40d	10d	-	+	+	+	+	-	-	+	+	-	-	+	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	1	-	1	-	-	-	1m	RO M	IAF	SS	SS IAF	G	6m G
31	Vijaya	58	F	June 2017	unemployed	25d	2d	-	+	+	+	+	-	-	-	+	+	-	+	-	-	+	6y	-	-	-	+	SLE Steroids	-	-	-	+	+	+	+	+	-	+	+	+	-	-	-	+	-	-	2	1	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	4m G
32	Chinnappa	40	M	July 2017	Farmer	35d	5d	-	-	-	-	-	-	-	-	+	+	-	-	-	+	+	3y	-	-	-	-	-	-	-	+	-	-	+	+	+	-	+	+	+	-	-	-	+	-	-	4	+	-	2g	-	-	-	RM	AF	MS	MSA F DC	G	6m G
33	Karnan	45	M	July 2017	Farmer	10d	3d	-	+	-	+	-	+	+	-	-	-	-	-	-	-	+	1y	-	-	+	-	-	-	-	-	-	+	+	+	-	+	+	-	-	+	-	-	2	-	1	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
34	Senthil Murugan	49	M	July 2017	Farmer	30d	0d	-	+	-	+	+	+	-	+	+	+	-	+	-	-	+	10y	-	-	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	-	3	4	1	1	2g	2g		-	RO M	AF	MS	MS AF MC	G	5m
35	Varalakshmi	36	F	July 2017	House wife	40d	10d	-	-	-	+	+	-	+	-	-	-	-	+	-	+	-	-	-	0	-	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	+	+	1	2	-	-	2g	-	-	-	RO M	AF	MS	MS AF	G	6m G
36	Jayaseelan	47	M	August 2017	Ad Agency	5d	1d	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	New	-	-	+	+	Hbs Ag	-	-	-	+	-	+	+	+	+	+	+	+	+	+	-	-	1	-	-	200 mg	-	-	-	RO CM	IAF	SS	SS IAF IMC	D	D
37	Mani	40	M	August 2017	Farmer	30d	0d	+	+	+	+	-	+	-	-	+	+	-	+	-	+	+	New	-	-	-	-	-	-	-	-	-	+	+	+	-	+	+	+	-	-	-	+	-	-	3	1	-	2g	-	-	6m	RO M	AF	MS	MS AF DC	G	6m G
38	Narasimhan	53	M	September 2017	Farmer	15d	5d	-	+	+	+	+	-	+	-	+	-	-	+	-	+	+	New	-	-	-	-	-	-	-	-	+	-	+	-	+	-	+	-	-	-	+	-	-	3	-	-	2g	-	3w	-	RO M	AF	MS	MS AF DC	G	6m G
39	Periyasami	34	M	September 2017	Farmer	35d	15d	-	+	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	1	-	1	2g	-	-	-	RO CM	AF	MS	MS AF	G	6m G
40	Saravanan	47	M	September 2017	Welder	25d	3d	-	+	-	+	+	+	+	+	+	+	+	+	-	-	+	7y	+	-	-	-	Rec	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	+	3	1	1	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
41	Yesuraj	50	M	September 2017	Farmer	10d	3d	+	+	+	-	+	+	+	+	+	-	+	+	-	-	+	1y	-	-	-	-	-	-	+	+	-	+	+	+	_	+	+	+	-	-	-	+	-	-	4	-	-	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
42	Manivasagam	55	M	October 2017	Farmer	8d	0d	+	+	-	+	+	+	+	+	+	-	-	+	-	+	+	2y	-	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	2	-	1	-	3g	6w	-	RO CM	AF	MS	MS AF MC HD	G	6m G
43	Poongavanam	43	M	October 2017	Farmer	10d	4d	+	+	-	+	+	+	+	+	+	+	-	+	-	-	+	3y	-	-	+	-	-	-	+	+	+	+	+	+	+	-	+	-	-	-	-	+	-	-	5	1	-	2g	-	4w	-	RO M	AF	MS	MS AF DC	G	6m healed
44	Deivanai	45	F	January 2018	House wife	30d	10d	-	-	-	+	-	+	+	-	-	-	-	-	-	+	+	1y	+	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	-	+	-	-	1	-	+	2g	-	-	-	RO CM	AF	SS	SS AF GC	G	6m G
45	Dhanabalan	54	M	February 2018	Driver	45d	0d	-	+	+	+	-	+	+	-	+	+	-	+	-	+	+	New	-	-	-	-	-	-	+	-	-	+	+	+	-	+	+	+	+	+	-	+	-	-	3	1	1	3g	-	-	-	RO CM	AF	MS	MS AF DC	G	6m G

S. No	Name	Age	Sex	Month of presentation	Occupation	Duration of illness	Treatmetnt Initiation	fever	nasal obstruction	nasal discharge	headache	Eye edema	Loss of vision	EOM fixed	proptosis	cheek swelling	palate	facial nerve	trigeminal nerve	altered gcs	Previous antibiotics	DM	duration	Regular Rx	control	DKA	Electrolyte Imbalance	Others	HT	Smoker	Alcoholic	Nephro	anaemia	eschar	pus	unhealthy mucosa	both nasal cavity	sinusitis	bone erosion	Retromaxillary area	orbital apex	cavernous sinus	Brain infarct	Only mucor	Mixed fungal	blood transfusion	debridement	maxillectomy	orbital decompression	ampho	liposomal ampho	posaconazole	itraconazole	Stage	Antifungals	Number of Surgery	Treatment stratergy	Outcome	Followup
46	Dhanalaxmi	62	M	February 2018	House wife	9d	1d	-	+	+	+	+	+	+	+	+	+	-	+	-	-	+	10y	-	-	+	-	Rec	-	-	-	-	+	+	+	+	-	+	+	+	-	-	+	-	+	3	1	-	2g	-	-	-	RO M	AF	MS	MS AF DC	G	6m G
47	Govindaraj	57	M	February 2018	Tempo Driver	20d	10d	-	-	-	+	-	-	-	-	+	+	-	+	-	+	+	8y	+	+	+	-	-	-	-	-	+	-	+	+	-	+	+	-	+	-	-	+	-	-	1	-	2g	-	-	3m	RM	AF	MS	MS AF DC	G	6m G
48	Thenmozhi	32	F	February 2018	House wife	20d	5d	+	+	+	+	-	-	-	-		=	+	+	+	-	+	2y	-	-	-	-	Rec	-	-	-	-	+	+	+	+	-	+	-	-	-	+	-	3	3	-	-	2g	-	-	-	RM	AF	MS	MS AF DC	G	2y G
49	Poongavanam	55	F	March 2018	House wife	20d	3d	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	7y	-	-	-	-	-	-	-	-	+	+	-	+	-	+	+	+	-	-	+	-	+	3	1	1	3g	-	-	-	RO M	AF	MS	MS AF DC	G	LTF
50	Venu	60	M	June 2018	House wife	10d	0d	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	15y	-	-	+	+	Hemipleg ia	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	2	1	-	2g	-	6w	-	RO CM	AF	MS	MS AF MC	G	4m G

Urkund Analysis Result

Analysed Document: Raghavi Dissertation Final.doc (D42783706)
Submitted: 10/19/2018 3:03:00 PM
Submitted By: raghavi281@gmail.com
Significance: 2 %

Sources included in the report:

https://pmj.bmj.com/content/80/949/670
https://academic.oup.com/cid/article/47/3/364/315276
https://cmr.asm.org/content/18/3/556
https://link.springer.com/article/10.1007/s00062-017-0629-1

Instances where selected sources appear:

14